Section 5: Effectiveness of Naturopathic Clinical Practice

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HIGHLIGHTS

- Naturopathic researchers have conducted original clinical research involving over 80 different illness populations.
- 81.1% of the studies on the effectiveness of naturopathic clinical practice identified a positive response to at least one primary or secondary outcome measure.
- Naturopathic cancer care includes managing primary symptoms of cancer and secondary symptoms associated with living with cancer, and/or adjunctive care during conventional cancer treatment.
- The risk of non-communicable diseases is strongly associated with modifiable risk factors – lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, dietary choices and environmental exposures – all of which are addressed as part of naturopathic care.
- The naturopathic individualized patient-centred approach to healthcare using a diverse range of therapies and practices is well suited in the prevention, treatment and management of a diverse range of conditions.
- Naturopaths/NDs have been instrumental in the development of integrative oncology, nutritional psychiatry and as fore-runners in recognizing the importance of gastrointestinal health in broader health issues.
- This section includes 235 original clinical research papers, yet due to the variety of complex interventions used by naturopaths/NDs further research is required on the effectiveness of naturopathic care.

Naturopaths/naturopathic doctors treat diverse physical and psychological health concerns throughout the full range of a patient's life. The majority of naturopathic visits focus on chronic diseases, but naturopathic clinicians also treat acute conditions and support patients in palliative care and those seeking advice for preventive medicine.

The chapters in this Section highlight the effectiveness of naturopathic care for conditions researched by the naturopathic profession and commonly treated by naturopaths/naturopathic doctors. While there are variations across topic areas, overall, 81.1% of the studies investigating the effectiveness of naturopathic treatments identified a positive response to at least one primary or secondary outcome measure. The clinical research presented in this section is based on work undertaken by naturopathic researchers across five WHO Regions. However, it is important to note that this is not the summation of research investigating clinical management of health conditions that is accessed and used by the naturopathic workforce. The diversity of knowledge and information used, shared and produced by naturopaths/NDs is described in more detail in Chapters 13 and 16.

The chapter on **Cancer and Cancer-related Conditions (Chapter 17)** describes the clinical research conducted by naturopaths investigating treatments for cancer and cancer-related conditions. Patients seeking naturopathic care for cancer support most commonly present with breast, colorectal, prostate and cervical cancer, but also include cancer survivors and individuals requiring palliative care. This section provides an overview of 53 clinical research papers investigating naturopathic treatments for cancer and cancer-related conditions, with 93.2% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on cancer is supplemented by over 100 observational studies and more than 60 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The conditions and populations investigated in these studies include:

- Breast Cancer
- Colorectal Cancer
- Prostate Cancer
- Other Cancers including lung and large B-cell lymphoma, hepatocellular carcinoma, endometrial and cervical cancer.
- Cancer patients requiring palliative care
- Cancer survivors

The chapter on **Cardiovascular Conditions (Chapter 18)** outlines the significant role that naturopaths/NDs

can have in the management of non-communicable diseases. This section provides an overview of 12 clinical research papers investigating naturopathic treatments for cardiovascular conditions, with 91% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on cardiovascular conditions is supplemented by over 20 observational studies and more than 20 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The cardiovascular conditions investigated in these clinical studies include:

- Hypertension
- Cardiovascular disease
- Post-cardiac surgery
- Other cardiovascular conditions including heart failure, venous leg ulcers and anemia

The chapter on **Complex Immune Conditions (Chapter 19)** outlines how the naturopathic approach of viewing the management of conditions through a lens of complexity, addressing multiple causative factors and physiological systems concurrently is beneficial for patients with complex immune conditions. This section provides an overview of 14 clinical research papers investigating interventions for complex immune conditions, including:

- HIV and AIDS
- Multiple sclerosis
- Chronic fatigue syndrome

The chapter on **Endocrine Conditions (Chapter 20)** describes the valuable current and future potential contribution of naturopaths/NDs assist with the treatment and prevention of endocrine conditions due in part, but not limited to, their specific training and focus on patient-centred lifestyle counselling. This section provides an overview of 23 clinical research papers investigating naturopathic treatments for endocrine conditions, with 91% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research investigating endocrine conditions is supplemented by 15 observational studies and 17 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The endocrine conditions include:

- Type II diabetes mellitus
- Metabolic syndrome
- Other endocrine conditions including pre-diabetes and obesity, hypothyroidism and hyperprolactinemia.

The chapter on **Gastrointestinal Conditions (Chapter 21)** describes gastrointestinal conditions as among the top reason patients seek naturopathic care. Naturopaths/NDs place a high importance on gastrointestinal health and recognize that it is linked to many other conditions. This section provides an overview of 17 clinical research papers investigating naturopathic treatments for gastrointestinal conditions, with 82.4% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on gastrointestinal conditions is supplemented by 13 observational studies and 39 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The gastrointestinal conditions investigated in these clinical studies include:

- Irritable bowel syndrome and functional gastrointestinal disorders
- Inflammatory bowel disease and coeliac disease
- Hepatobiliary and pancreatic conditions
- Other gastrointestinal conditions including gastrointestinal infections and dyspepsia.

The chapter on **Mental Health Conditions (Chapter 22)** highlights the value of the naturopathic broad-spectrum approach to health and disease and application of the naturopathic principle *Treat the Whole Person* when providing care to patients with mental health disorders by acknowledging the significance of a person's mental status when treating any condition. This section provides an overview of 34 clinical research papers investigating naturopathic treatments for mental health conditions, with 64.7% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research investigating mental health conditions is supplemented by over 50 observational studies and more than 80 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The research in mental health has focused on several naturopathic interventions with herbal medicines, nutraceuticals and yoga having the most notable clinical effects. The mental health conditions investigated in these clinical studies include:

- Depression
- Anxiety
- Other mental health conditions such as obsessive-compulsive disorders, schizophrenia and psychotic disorders.

The chapter on **Musculoskeletal Conditions (Chapter 23)** outlines naturopaths/NDs broad treatment approach with musculoskeletal conditions, which are among the primary complaints of patients consulting with naturopaths/ND. This section provides an overview of 30 clinical research papers investigating naturopathic treatments for musculoskeletal conditions, with 89.3% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on MSK conditions is supplemented by over 50 observational studies and more than 50 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The musculoskeletal conditions include:

- Chronic neck pain
- Low back pain

- Osteoarthritis
- Fibromyalgia
- Other musculoskeletal conditions including heel pain, temporomandibular joint pain and rotator cuff tendonitis.

The chapter on **Neurological Conditions (Chapter 24)** describes the diverse treatment approach used by naturopaths/NDs in the treatment of neurological conditions. It also provides an overview of 21 clinical research papers investigating interventions for neurological conditions, with 66.7% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research on neurological conditions is supplemented by more than 40 observational studies and 25 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. The neurological conditions investigated in these clinical studies include:

- Migraines and chronic headaches
- Parkinson's disease
- Other neurological conditions including ADHD, Alzheimer's disease, Autism spectrum disorders, traumatic brain injuries and trasverser myelitis.

The chapter on **Skin Conditions (Chapter 25)** outlines the importance that naturopaths/NDs place on the appropriate management of skin conditions as naturopathic theory identifies the skin as the largest detoxification of the body and as a representation of internal health. This chapter provides an overview of eight clinical research papers investigating naturopathic treatments for skin conditions, with 62.5% reporting a positive outcome in at least one primary or secondary outcome. The skin conditions investigated in these clincal studies include:

- Acne vulgaris
- Psoriasis
- Vitiligo vulgaris
- Other skin conditions such as dermatitis and plantar warts

The chapter on **Women's Health Conditions (Chapter 26)** describes the central role of effective management of women's health conditions, with over 70% of the patients seeking naturopathic care being female. It provides an overview of 11 clinical research papers investigating naturopathic treatments for women's health conditions, 81.8% reporting a positive outcome in at least one primary or secondary outcome. This body of naturopathic research is supplemented by over 40 observational studies and more than 30 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28. To date the research has primarily focused on herbal and dietary interventions with herbal treatments having the most notable clinical effects. The women's health conditions investigated in these clinical studies include:

- Menopausal symptoms
- Menstrual disorders
- Polycystic Ovarian Syndrome
- Other women's health conditions including recurrent pregnancy loss, vaginal candidiasis and interstitial candidiasis.

The chapter on **Other Conditions (Chapter 27)** overviews 14 clinical research papers investigating naturopathic treatments for a range of other conditions, with 85.7% reporting a positive outcome in at least one primary or secondary outcome. The other conditions investigated in these clinical studies include:

- Overweight or obesity
- Respiratory conditions including pulmonary tuberculosis, asthma, chronic rhinosinusitis, common cold
- Genitourinary conditions including sexual dysfunction, urinary incontinence

The chapter on **Other Research Publications Related to Health Conditions (Chapter 28)** presents a summary of over 1,456 health condition-related non-clinical research articles published by naturopathic researchers in indexed peer-reviewed journals. Approximately half of these articles are reviews and meta-analyses (n=357; 24.5%) or observational studies (n=363; 24.9%). These types of articles present an important contribution to the understanding of health, illness, and its management. This reinforces the knowledge translation behaviours of naturopaths/NDs (outlined in Chapter 13) through which research from many areas of health and medicine may be used by naturopaths/NDs to inform clinical decisions.

Overall, this Section:

- Presents the results of 235 original clinical research articles including randomized-controlled trials (n=145), uncontrolled trials (n=34), case reports (n=34), cohort studies (n=9), secondary analyses (n=5) and non-randomized controlled studies (n=4).
- Features clinical studies that commonly employ pragmatic elements such as multi-modal interventions, flexibility in administration, and real-world settings.
- Demonstrates investigation by the naturopathic workforce of a full range of naturopathic therapeutic modalities and practices including clinical nutrition (n=58), herbal medicines (n=44), yoga (n=36), acupuncture and cupping (n=30), applied nutrition (n=29), complex naturopathic interventions (n=22), lifestyle modifications (n=17), hydrotherapy (n=13), mind-body medicine (n=9), naturopathic physical medicine (n=9), homeopathy (n=5) and a range of other inventions (n=12).

17 Cancer and Cancer-related Conditions

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HIGHLIGHTS

- Individuals with cancer who consult with a naturopath/naturopathic doctor most commonly present with breast, colorectal, prostate or cervical cancer. As well as providing direct support during cancer treatment, these individuals may also seek assistance with recovery from cancer or palliative care.
- Naturopathic care for individuals with cancer includes managing primary symptoms of cancer and secondary symptoms associated with living with cancer, and/or adjunctive care during conventional cancer treatment.
- The risk of cancer is strongly associated with modifiable risk factors – lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, dietary choices and environmental exposures – all which are addressed as part of naturopathic care.
- The naturopathic individualized patient-centred approach to healthcare using a diverse range of therapies and practices is well suited in the prevention, treatment and management of cancer.
- 93.2% of the clinical research investigating naturopathic interventions for cancer and cancer-related conditions reported a positive outcome in at least one primary or secondary outcome measure

Globally, cancer accounts for an estimated 10 million deaths in 2020, and is one of the top leading causes of premature death in 134 of 183 countries [1, 2]. The World Health Organization (WHO) defines cancer as a large group of diseases that can start in almost any organ or tissue when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and/or spread to other organs [1].

Risk factors associated with cancer development can be categorized as modifiable and non-modifiable. The latter are factors that are intrinsic and immutable such as age, sex and certain genetic considerations [3]. Modifiable risks have the benefit of typically being at least somewhat influenced by individual variability and within cultures. In many ways the modifiable risk factors are similar to those associated with other non-communicable diseases (NCDs) and include: lifestyle-related activities that can lead to prolonged ultra-violet exposure; diet and nutrition choices; alcohol consumption; sedentary behaviour and obesity; tobacco use; and environmental exposure to pollutants (heavy metals and chemicals), contaminated air, water, soil and food; ionizing radiation and infectious or hazardous agents [2, 4, 5].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=47; published in 53 papers) naturopathic researchers have conducted involving populations with cancer or those at risk of cancer. This research includes a total of 5,879 participants and was conducted in the United States of America (USA) (n=33), India (n=13), Germany (n=3), Australia (n=2) and New Zealand (n=2). The research designs used in these studies include randomized controlled trials (n=35), cohort studies (n=6), uncontrolled trials (n=4), case reports (n=2) and secondary analysis (n=6). The study interventions featured a range of therapeutics including clinical nutrition (n=11), yoga (n=10), applied nutrition (n=8), herbal medicines (n=7), acupuncture/acupressure (n=7), exercise/lifestyle (n=6), mind-body medicine or psychological counselling (n=5), homeopathy (n=1), and conventional medicine practices including a triage coding system for palliative care (n=1).

The conditions examined included breast cancer (n=24), colorectal cancer (n=5), prostate cancer (n=3), cervical cancer (n=1) and other cancers (n=3), as well

as studies on palliative care (n=1) and cancer survivors (n=17). Of all the naturopathic clinical studies examining cancer populations, 93.2% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 17.1: Clinical research investigating cancer conducted by naturopathic researchers*. This body of naturopathic research on cancer is also supported by over 100 observational studies and more than 60 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Naturopathy/naturopathic medicine is supported by evidence to provide multiple interventions in an integrative model to support the whole person on the cancer continuum while considering the type of cancer, and all stages of the disease including prevention. To date, naturopathic research has primarily focused on breast cancer which is likely an outcome of the high prevalence of breast cancer worldwide and the high prevenance of female patients that seek naturopathic services [6]. The main interventions that have been examined by naturopathic researchers in the cancer continuum include yoga, applied nutrition (diet), clinical nutrition and acupuncture/acupressure.

Naturopaths/naturopathic doctor are well suited for cancer-related care as they are trained to support individuals to make meaningful and beneficial changes to modifiable risk factors. Cancer support is among the top ten conditions for which patients seek naturopathic care, with the majority seeking assistance for supportive care during cancer treatment, naturopathic care during recovery, and primary prevention of cancer or its recurrence [7].

Naturopathy/naturopathic medicine is a system of healthcare that is an exemplar of the type of care applied within the burgeoning field of integrative oncology – *"a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment"* [8]. When working with a patient undergoing cancer care, and in line with the philosophy of holism, naturopaths/naturopathic doctors aim to assess and manage the whole person throughout the cancer care continuum. This includes managing the primary symptoms of cancer, and potential secondary symptoms that are often associated with living with cancer and/or the negative side effects of conventional cancer treatment [9, 10].

Naturopaths/naturopathic doctors are actively involved in, and have led in the establishment of, the Society of Integrative Oncology (SIO) – a multidisciplinary international group of health professionals committed to integrative cancer-related care. A substantive proportion of contributions by naturopathic clinicians and researchers in this field has come from Canada and the United States. The Oncology Association of Naturopathic Physicians (OncANP), dedicated to the growth and development of naturopathic oncology, have developed a comprehensive overview of naturopathic guidelines related to supportive cancer care [11]. The guidelines outline principles of integrative oncology that are based on sound ethical and evidence-informed approaches for naturopaths/naturopathic doctors who provide care to patients diagnosed with cancer. These principles are designed, in part, to increase interprofessional dialogue and encourage a more integrative approach to care for those living with cancer [12].

Cancer is a complex condition in which each cancer type, subtype and ultimately, each person requires an individual treatment approach. The naturopathic principle of treating the whole person effectively models the naturopathic person-centered care that can improve patient outcomes and quality of life. The naturopathic approach considers the psychosocial state, a patient's mental and emotional wellbeing, and quality of life measures. It also takes into consideration symptoms commonly associated with cancer care including, but not limited to nausea and vomiting, gastrointestinal dysfunctions, mucositis, xerostomia, dysgeusia, neuropathy, insomnia, iatrogenic menopause, pain, fatigue, impacts to mobility and functional changes, immune compromise and cytopenia all of which can be an outcome of the cancer, or negative effects from conventional treatment [10, 13]. Although further research is required, evidence points to a promising role of naturopaths/naturopathic doctors as integral members of integrative oncology teams. As cancer moves towards the number one NCD, research highlights the role naturopaths/naturopathic doctors can have within the medical system towards providing more holistic and comprehensive cancer care and strategies for prevention.

Studies investigating specific conditions:

Breast Cancer

The predominant type of cancer that naturopathic researchers have studied is breast cancer. The 21 studies (25 published papers) [14-38] mostly examined interventions involving non-metastatic breast cancer populations undergoing conventional adjuvant treatment (chemotherapy and/or radiation) (n=18: 22 published papers)

[14-29, 31-34, 36, 37] , and one study investigated breast cancer risk [15]. Only two trials included participants with metastatic disease [30, 35]. Yoga was the most common researched intervention (n=9; 12 published papers) [14, 24-30, 33-36], followed by clinical nutrition (n=5; 7 published papers) [18, 20-22, 31, 32, 38], acupuncture/acupressure (n=4) [16, 17, 19, 23] and herbal medicine (n=1) [37].

Clinical finding

Integrated yoga practice may reduce the side effects of chemotherapy, increase quality of life and reduce post-surgical hospital stays in individuals with breast cancer.

A randomized controlled trial conducted in India [24] investigated the outcomes of an integrated yoga practice (including *asanas*, *pranayama*, and meditation and relaxation techniques) concurrent to 4-6 cycles of chemotherapy among individuals with stage II and III operable breast cancer experiencing chemotherapy-induced nausea and vomiting (n=62). The intervention was compared with a psychotherapy technique. Compared to the control group, participants in the yoga group reported reduced nausea frequency (-0.9, p=0.01) and intensity (-1.1, p<0.001) and reduced vomiting frequency (-0.6; p=0.06) and intensity (-0.6; p=0.05). They also reported reduced levels of anxiety (State Trait Anxiety Inventory [STAI]: -8.3; p<0.01) and increased quality of life (Functional Living Index for Cancer – Overall quality of life: +30.4, p<0.001). After the fourth cycle of chemotherapy, the yoga group also reported reduced number (-3.3; p=0.002) and severity (-9.7; p<0.001) of symptoms compared to the control group, as well as reduced symptom-associated distress (-13.3; p<0.001) and reduced chemotherapy toxicity (-3.8; p<0.001).

A second randomized controlled trial conducted in India [27] also investigated a yoga intervention compared with supportive counselling and postoperative exercise rehabilitation for four weeks (one week before surgery and three weeks post-surgery) for individuals with stage II and III breast cancer (n=69). The study found participants in the yoga arm had a greater reduction in anxiety (STAI-state: -10.2, p<0.04; STAI-trait: -9.4, p<0.01) and depression (Beck's Depression Inventory: p=0.08), and an increased quality of life (Functional Living Index of Cancer: p=0.01), compared to the control group. The control group also had an increase in levels of Immunoglobulin A (+0.64, p=0.001) and a reduction in lymphocytes (CD4+: -3.5, p=0.002; CD8+: -3.7, p=0.001; CD56+: -4.3, p=0.001) indicating weaker immune status, compared to the participants in the yoga group. Secondary analysis from this study [26] further found the yoga group were in the hospital (-1.3; p=0.003) fewer days, had a reduction in drain retention post-surgery (-1.74; p=0.001) and decreased number of days needed to wait for suture removal (-2.4; p=0.031). Further analysis also reported reduced depression post-surgery (p<0.01) as well as during and after radiotherapy (p<0.001) and chemotherapy (p<0.001) [28].

A randomized placebo-controlled trial conducted in the USA investigated omega-3 fatty acids (3.3g per day) over 24 weeks for the treatment of joint pain among women with breast cancer (n=249) [21, 22]. Primary data analysis [21] found no difference in the primary or secondary outcomes (i.e., Brief Pain Inventory [BPI], Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC], modified score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands [AQCRAH], Functional Assessment of Cancer Therapy – Endocrine [FACT-E]), except for reduced serum triglyceride levels in the intervention group (-22.1 vs -10.3, p=0.01). However, the research team conducted sub-analyses [22] based on participant body mass index (BMI) and found that participants with a BMI ⩾30 had improvements at the end of the study period on several domains of the BPI including reduced worst pain (p=0.02), reduced average pain (p=0.002), and reduced pain interference (p=0.05) when taking omega-3 fatty acids compared to placebo. These reductions in pain were also supported by reduced end-of-study scores for WOMAC (p=0.01) and AQCRAH (p=0.04).

Colorectal Cancer

The colorectal cancer studies were conducted in the USA [39-43] (n=5) and Germany [44] (n=1). The studies investigated *Zingiber officinale* (ginger) (n=4) [39-42], dietary and physical activity counselling (n=1) [43] and yoga (n=1) [44].

Clinical finding

Ginger *(Zingiber officinale)* may reduce the risk of colorectal cancer.

One randomized placebo-controlled trial conducted in the USA investigated the effects of 1000mg twice per day of *Zingiber officinale* (standardized to 5% gingerols) for 28 days on otherwise healthy adults with identified colorectal cancer risk (n=21) [39]. The study found no difference in surrogate markers for apoptosis or differentiation, however, proliferation markers were reduced (whole crypts: -41.2%, p=0.05; differentiation zone: -47.9%, p=0.04) and there was evidence of increased apoptosis relative to proliferation (+25.6%, p=0.05). A second placebo-controlled randomized trial conducted in the USA (n=50) examined 2000 mg of *Zingiber officinale*

daily for 28 days among individuals with either normal or high risk of colorectal cancer. Participants with high risk scores were found to have reduced COX-1 protein levels that are associated with early event of colorectal cancer by 23.8% among the *Zingiber officinale* group versus 18.9% in the placebo arm (p=0.03) [40].

One uncontrolled trial conducted in Germany (n=54) [44] found that 90 minute weekly classes of yoga for 10 weeks improved participants' emotional well-being (+1.59, p=0.019), as measured by the Functional Assessment of Cancer Therapy – Colorectal (FACT-C), but not other FACT-C domains. The study participants also reported reduced anxiety (Hospital Anxiety and Depression Scale [HADS]: -1.14, p=0.034) and depression (HADS: -1.34, p=0.038) at the end of the intervention period, and reduced sleep disturbance (Pittsburgh Sleep Quality Index: -1.08, p=0.043) at Week 12.

Prostate Cancer

Three studies from New Zealand (n=1) [45], USA (n=1) [46] and Australia (n=1) [32], one of which included secondary analyses [47], investigated naturopathic treatment interventions for patients with prostate cancer. The studies investigated interventions involving clinical nutrition (n=2) [32, 46] and applied nutrition (n=1) [45, 47].

An uncontrolled study conducted in New Zealand examined the effect of the Mediterranean diet on 20 men with prostate cancer over a period of 3 months [45]. The main outcomes were a bloodspot fatty acid profile and alkaline single-cell gel electrophoresis pre- and post-intervention. The fatty acid profile found reduced saturated fatty acids and increased omega-3 fatty acids both as true values and in relation to each other (total saturated fatty acid (SFA) level: 34.7% vs 33.7% (p=0.002); 18:0 stearic acid 10.5% vs 10%, p=0.002; 2:5 omega-3 docosohexanoic acid [DHA] 3.0% vs. 3.5%, p=0.01; eicosapentanoic acid [EPA]:DHA ratio 4.4% vs. 5.0%, p=0.042; omega-3 index 6.1% vs. 7.0%, p=0.043; omega-6 polyunsaturated fatty acids [PUFA]:omega-3 PUFA 5.2% vs. 4.7%, p=0.019; and arachidonic acid [AA]:EPA 8.58% vs 6.9%, p=0.030. Based on the alkaline single-cell gel assay, DNA damage was inversely correlated with dietary adherence (p=0.013), whole blood monounsaturated fatty acids (p=0.009) and oleic acid (p=0.020). DNA damage correlated with the intake of dairy products (p=0.043), red meat (p=0.007) and whole blood omega-6 PUFA (p=0.015) [45]. Follow up analysis from this study, published in a second paper [47], included testing for prostate-specific antigen (PSA), C-reactive protein (CRP) and additional outcomes assessed by the alkaline single-cell gel assay. In this, no correlation was seen between adherence to a Mediterranean diet and PSA or CRP. From the alkaline single-cell gel assay, a significant reduction in DNA damage was found in men who adhered to the diet (p=0.013) or had high levels of folate intake (p=0.023), vitamin C (p=0.007), legumes (p=0.004) and green tea (p=0.002). Similarly, the authors reported an inverse relationship in DNA damage with both higher red meat (p=0.003) and dairy consumption (p=0.008) intake [47].

A retrospective cohort study conducted in the United States also sampled patients with prostate cancer (n=139) of whom 69 participants had received 24 months of naturopathic care which most commonly consisted of supplementation with green tea extract, melatonin, vitamin C and vitamin E. Participants' PSA was evaluated 6-8 weeks after receiving radiation therapy with curative intent and found no change (including no increases) to their PSA compared to participants receiving usual care [46].

Other Cancers

Other cancers, including: lung and large B-cell lymphoma [32], hepatocellular carcinoma [48], endometrial [32] and cervical cancer [49] were studied by naturopathic researchers. One study included six different cancer populations in the same study [32].

Clinical finding

B vitamins may lower chemotherapy-induced peripheral neuropathy in individuals with cancer undergoing chemotherapy treatment.

This latter study was a randomized controlled trial conducted in Australia which examined the effects of a B-group vitamin complex on the development of chemotherapy-induced peripheral neuropathy [32]. The study participants (n=71) were diagnosed with a range of primary cancers (i.e., breast, lymphoma, lung, colon, prostate, and endometrial) and were undergoing chemotherapy. They were administered the intervention or a placebo one week before chemotherapy and continued for 12 weeks after chemotherapy was completed. While the primary outcome of the study – total neuropathy score – was not significantly different between groups, participants in the intervention group did have lower sensory neuropathy scores compared to placebo at different time points in the study (Wk 2: p=0.03, Wk 24: p=0.005; Wk 36: p=0.021). The lymphoma patients enrolled in this trial (n=20) found that 1000mcg of vitamin B12 during treatment and three months post-chemotherapy prevented the onset and severity of vincristine-induced peripheral neuropathy. This regime was found to be most beneficial with a chemotherapy combination of cyclophosphamide, doxorubicin, vincristine and rituximab (R-CHOP) every 3 weeks for 8 cycles. Vitamin B12 was found to be safe and efficacious when used concurrently with R-CHOP in large B-cell lymphoma patients [32].

Palliative care

One cohort study conducted in India involving palliative care patients (n=506) assessed a triage-based coding system for home based palliative care [50]. They used a multidisciplinary team inclusive of a palliative care physician and a naturopathic clinician, who assessed and managed pain, physical symptoms, and psychosocial issues. Of the 506 patients, 32 (6.32%) were considered high priority, 105 (20.75%) medium priority and 369 (72.92%) low priority. In both high and medium priority patients, comparison of Edmonton Symptom Assessment Scale (ESAS) scores during the first and second home visits found significant improvements in pain (high: -6; medium: -3; $p<0.001$), fatigue (high: -4; medium: -5; $p<0.001$), nausea and vomiting (high: -3; medium: -5; $p<0.001$), loss of sleep (high: -2; medium: NS; $p<0.001$), breathlessness (high: -2; medium: -7; $p<0.001$), loss of appetite (high: -3; medium: -5; $p<0.05$), and loss of well-being (high: -7; medium: -5; $p<0.001$). The improved pain and symptom control for these patients assisted in avoiding hospital deaths; time taken for intervention triaging and was a significant predictor of survival [50].

Cancer survivors

Twelve studies involved cancer survivors [43, 51-61] with five publishing additional analyses of their results [62-66]. The studied interventions included applied nutrition and/or lifestyle (n=5; 8 published papers) [43, 54, 56, 57, 60, 63, 64, 66], clinical nutrition (n=2; 3 published papers) [52, 55, 62], acupuncture (n=2; 3 published papers) [59, 61, 65], yoga (n=1) [51], mind-body medicine (n=1) [53], and homeopathy (n=1) [58].

A randomized controlled trial conducted in the USA [54, 66] provided nine sessions of nutrition education, cooking classes and food shopping field trips for Hispanic breast cancer survivors (n=70) over 12 weeks. Participants in the control arm of the study received written dietary recommendations. The study found, compared to the control, participants in the intervention group had a greater increase in intake of target fruit and vegetables after the intervention period (fruit: +2.0 vs 0.0, $p=0.004$; vegetable: +1.2 vs -0.2, $p=0.001$) and at three months follow up (fruit: +2.7 vs +0.5, $p=0.002$; vegetable: +1.8 vs +0.6, $p=0.02$), and similar results for total fruit (Mth 3: +1.1 vs -0.3, $p=0.05$; Mth 6: +2.0 vs -0.1, $p=0.002$) and vegetable (Mth 3: +1.1 vs -0.4, $p=0.004$; Mth 6: +1.8 vs +0.2, $p=0.005$) intake. Participants in the intervention arm also reported reduced caloric intake compared to control (Mth 3: -672.9 vs -92.4, $p<0.0001$; Mth 6: -562.9 vs +61.6, $p<0.001$) over the study period and reduced waist circumference after the intervention (-1.6 vs +1.7, $p=0.05$), but not at the end of the follow up period.

A cohort study conducted in Germany investigated a mindfulness-based stress reduction program that incorporated the Mediterranean diet and naturopathic interventions including poultice use, phytotherapy, massage and hydrotherapy for adult cancer survivors (n=117) [53]. Six hourly sessions were given weekly for 11 weeks with a three month follow up. The researchers found that participants' quality of life increased significantly in the domains of general health (+8.73, $p=0.001$), cognitive function (+7.42, $p=0.001$), and social function (+13.11, $p=0.001$). In addition, the intervention program improved role function (+14.07, $p<0.001$) and emotional function (+13.22, $p<0.001$) while reducing fatigue (-9.63, $p=0.009$), pain (-9.38, $p=0.033$), constipation (-5.02, $p=0.033$), and insomnia (-17.13, $p<0.001$). It also reduced anxiety (-2.31, $p<0.001$) and depression (-1.94, $p<0.001$) and had significantly increased life satisfaction (-3.04, $p<0.001$), health satisfaction (+1.95 $p<0.001$) and mindfulness (+4.29, $p<0.001$).

A randomized control trial from the USA assessed the impact of acupuncture among 43 adult survivors of cancer with symptoms of persistent cancer-related fatigue 12 weeks post cancer treatment [59]. The intervention compared three different acupuncture treatments: high-dose stimulatory acupuncture (HIS), low-dose stimulatory acupuncture (LIS) and relaxation acupuncture (RA). Based on the Brief Fatigue Inventory scale all groups experienced a reduction in fatigue severity, but the greatest improvement was in the relaxation groups (HIS: -2.2; LIS: -2.7; RA: -4.0) compared to other groups ($p=0.027$).

Table 17.1 Clinical research investigating cancer and cancer-related conditions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Banerjee, et al. (2007) [India, SEARO] [14]	Randomized controlled trial	Breast cancer (undergoing radiotherapy or adjuvant chemotherapy or radiotherapy)	Yoga (guided meditation, *asanas*, *pranyama*, *nidra* chanting)	6 weeks (90 min, progressive sessions)	Supportive counselling and light exercise	68 (35/33)	Hospital Anxiety and Depression Scale [BL to Wk 6, pre and post radiation]	**Reduced anxiety** Yoga (-4.4, p<0.001) Control (+2.3, p<0.001) **Reduced depression** Yoga (-4.6, p<0.001) Control (+1.9, p<0.001)
							Perceived Stress Scale [BL to Wk 6, pre and post radiation]	**Reduced stress** Yoga (-5.5, p<0.001) Control (+1.4, p<0.001)
							Radiation-induced DNA damage – Alkaline Single-Cell Gel Electrophoresis (Comet) Assay [BL to Wk 6, pre and post radiation]	**Reduced DNA damage** Yoga (+21.7, p<0.001) Control (+26, p<0.001) Between groups difference 14.5% (p<0.001)
Bishop, et al. (2015) [New Zealand, WPRO] [45]	Uncontrolled trial	Prostate cancer	Mediterranean style diet. Light to moderate exercise was encouraged	3 months (30 – 50 g seeds and nuts daily; ⩾15 mL or more of extra virgin olive oil; ⩽1 portion dairy daily; substitute butter/margarine with olive oil-based spread; ⩽400g/wk red meat, substitute with oily fish and white meat; avoid processed meats; eat oily fish ⩾ once/wk)	Nil	20	Holman Bloodspot fatty acid profiles [pre and post intervention]	**Reduced saturated fatty acids** Mean total SFA (-1.0, p=0.002) 18:0 stearic acid (-0.5, p=0.002) n6PUFA:n3PUFA (-0.6, p=0.019) AA: EPA (-1.6, p=0.030) **Increased omega-3 fatty acids** 22:5 n3 DHA (+0.5, p=0.01) EPA / DHA (+0.6, p=0.042) Modified WBS n3 index (+0.9, p=0.043)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
Erdrich, et al. (2015) [New Zealand, WPRO] [47]	Secondary analysis						Alkaline Single-Cell Gel Electrophoresis (Comet) Assay [pre and post intervention]	**Reduced DNA damage** DNA damage inverse correlation with dietary adherence (p=0.013) whole blood monounsaturated fatty acids (p=0.009) and oleic acid (p=0.020) DNA damage positive correlation with intake of dairy products (p=0.043) red meat (p=0.007) and whole blood n6PUFA (p=0.015)
							Body weight (kg) [BL to 3 Mths]	**Reduced body weight** -2.3 kg, (p=0.0007)
							BMI [BL to 3 Mths]	**Reduced BMI** -0.85kg/m^2, (p<0.001) BMI was inversely correlated to blood n3PUFA (p=0.046). Reduced BMI associated with increased blood PUFA (p=0.031) and LA (p=0.040).
							Changes in the sources of dietary fat [BL to 3 Mths]	**Increased dietary fat** olive oil (+14.2, p=0.0008) nuts (+2.9, p=0.0003) fish (+1.8, p=0.0005) Reduced dairy (-2.9, p=0.0025) and red meat (-2.0, p=0.0005)
							Holman Bloodspot fatty acid profiles (mean %) [BL to 3 Mths]	**Reduced saturated fatty acids** Mean total SFA (-1.0, p=0.002) 18:0 stearic acid (-0.5, p=0.002) n6PUFA:n3PUFA (-0.6, p=0.019) AA: EPA

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								(-1.6, p=0.030) **Increased omega-3 fatty acids** 22:5 n3 DHA (+0.5, p=0.01) EPA / DHA (+0.6, p=0.042) Modified WBS n3 index (+0.9, p=0.043)
							C reactive protein [BL to 3 Mth, relative to Dietary Adherence Questionnaire]	NS
							Prostate-specific antigen [BL to 3 Mth, relative to Dietary Adherence Questionnaire]	NS
Bowen, et al. (2006) [USA, AMRO] [15]	Randomized controlled trial	Breast cancer risk	Group psychological counselling	4 weeks (2-hour sessions, follow up 6 months and 24 months)	Waitlist control	150 (81/69)	Breast cancer screening – mammography [BL to Mth 24]	**Increased screening** Mth 24 ⩾40yo: +12% (p<0.05)
							Breast cancer screening – (breast self-exam) [BL to Mth 6, Mth 24]	**Increased screening** Mth 6: +17% (p<0.01) Mth 24: +13% (p<0.05)
							Perception of lifetime personal breast cancer risk [BL to 6mth, 24mth]	**Reduced perception of risk** Mth 6: -20%; Mth 24: -21% Over time: p<0.001 Between group: p<0.001
							Cancer Worry Scale [BL to 6mth, 24mth]	**Reduced worry** Mth 6: -0.7; Mth 24: -0.7% Over time: p<0.001 Between group: p<0.001
							Short Form-36 Health Survey [BL to 6mth, 24mth]	**Increased quality of life** Mth 6: +4.6; Mth 24: +5.1 Over time: p<0.001 Between group: p<0.01

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Braun, et al. (2013) [USA, AMRO] [46]	Cohort study (retrospective investigation)	Prostate cancer (post-treatment of 6-8 wks radiation therapy with curative intent)	Individualized naturopathic and nutritional antioxidant supplementation (self-selected for naturopathic care)	24 months (most frequently given: green tea extract 750 BD, melatonin 20mg bedtime, vitamin C 500-1000mg TD, vitamin E 200-400IU TD)	Usual care control (self-selected for no naturopathic care)	134 (69/65)	Mean PSA (non hormonal ablation) [⩾ 24 mths post-radiation]	NS
							Mean PSA (hormonal ablation) [⩾ 24 mths post-radiation]	NS
Citronberg, et al. (2013) [USA, AMRO] [39]	Randomized controlled trial	Colorectal cancer risk (otherwise healthy adults)	*Zingiber officinale* (radix) standardized 5% ginergols	28 days (four 250mg cap twice per day)	Placebo	21 (10/11)	Apoptosis markers (Bax and Bcl-2 expression) [BL to Wk 4]	Apoptosis promotion (Bax): NS Apoptosis inhibition (Bcl-2): NS Bax:Bcl-2 ratio: NS
							Differentiation marker (p21) [BL to Wk 4]	NS
							Proliferation markers (hTERT and MIB-1 expression) [BL to Wk 4]	**Reduced proliferation** hTERT Whole crypts: -41.2% (p=0.05) Differentiation zone: -47.9% (p=0.04) Proliferation zone: NS MIB-1: NS
							Relative effects (ratio of p21:hTERT, p21:MIB-1, Bax:hTERT, Bax:MIB-1) [BL to wk 4]	**Increased apoptosis relative to proliferation** Bax:hTERT: +25.6% (p=0.05) Bax:MIB: NS Differentiation relative to proliferation: NS
Cramer, et al. (2015) [Germany, EURO] [51]	Randomized controlled trial (open label)	Menopausal symptoms (breast cancer survivors)	Hatha yoga and Tibetan Buddhist meditation	12 weeks (90 min, weekly)	Usual care control	40 (19/21)	Menopausal Rating Scale (MRS) – Total score [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -5.6 (p=0.004) Wk 24: -4.5 (p=0.023)
							MRS – Somatovegetative symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -1.8 (p=0.035) Wk 24: -1.9 (p=0.028)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							MRS – Psychological symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -2.4 (p=0.012) Wk 24: NS
							MRS – Urogenital symptoms [BL to Wk 12, 24]	**Reduced symptoms** Wk 12: -1.5 (p=0.025) Wk 24: -1.3 (p=0.025)
							Functional Assessment of Cancer Therapy – Breast (FACT-B) – Total score [BL to Wk 12, 24]	**Increased function** Wk 12: +12.5 (p=0.002) Wk 24: +12.6 (p=0.004)
							FACT-B – Physical function [BL to Wk 12, 24]	**Increased function** Wk 12: NS Wk 24: +3.6 (p=0.01)
							FACT-B – Social function [BL to Wk 12, 24]	**Increased function** Wk 12: +2.4 (p=0.24) Wk 24: +2.6 (p=0.16)
							FACT-B – Emotional function [BL to Wk 12, 24]	**Increased function** Wk 12: +2.8 (p=0.005) Wk 24: +1.6 (p=0.036)
							FACT-B – Functional [BL to Wk 12, 24]	**Increased function** Wk 12: +3.3 (p=0.024) Wk 24: NS
							FACT-B – Breast cancer-specific [BL to Wk 12, 24]	NS
							Functional Assessment of Chronic Illness Therapy – Fatigue [BL to Wk 12, 24]	**Increased energy** Wk 12: +6.0 (p=0.10) Wk 24: (7.3, p=0.012)
							Hospital Anxiety and Depression Scale [BL to Wk 12, 24]	Anxiety: NS Depression: NS
Cramer, et al. (2016) [Germany, EURO] [44]	Randomized controlled trial (open label)	Colorectal cancer (stage I-III)	Hatha yoga, *pranayama* breathing, meditation, *yoga nidra*	10 weeks (90 min weekly class)	Waitlist control	54 (27/27)	Functional Assessment of Cancer Therapy – Colorectal [BL to Wk 10, 22]	**Increased emotional wellbeing** Wk 10: NS Wk 22: Emotional: +1.59 (p=0.019) Physical: NS Social: NS Functional: NS Colorectal cancer-specific: NS Total: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							Functional Assessment of Chronic Illness Therapy [BL to Wk 10, 22]	Fatigue: NS Spiritual wellbeing: NS
							Sleep disturbance – Pittsburgh Sleep Quality Index [BL to Wk 10, 22]	**Reduced sleep disturbance** Wk 10: NS Wk 12: -1.08 (p=0.043)
							Hospital Anxiety and Depression Scale [BL to Wk 10, 22]	**Reduced** Wk 10: Anxiety: -1.14 (p=0.034) Depression: -1.34 (p=0.038) Wk 22: NS
							Bodily awareness and dissociation – Scale of Body Connection [BL to Wk 10, 22]	NS
							Treatment expectancy – Body-Efficacy Expectation Scale [BL to Wk 10, 22]	NS
Crew, et al. (2007) [USA, AMRO] [16]	Randomized controlled trial (crossover)	Breast cancer stage I-IIIa hormone receptor positive – joint pain associated with adjuvant aromatase inhibitor therapy	Acupuncture on TW5, GB41, GB34, LI4, ST41, KD3, auricular acupuncture, and joint-specific protocols for shoulder, wrist, fingers, lumbar, hip, and knee (30 min, twice per wk for 6 wks)	6 weeks (30 min, twice per week)	Observation with non-narcotic, non-steroidal pain medications as needed	19	Brief Pain Inventory – short form [BL to Wk 6]	**Reduced** Pain scores: -3.1 (p=0.01) Pain severity: -2.7 (p=0.02) Functional interference: -1.4 (p=0.02)
							Western Ontario and McMaster Universities Osteoarthritis index [BL to Wk 6]	**Reduced impact on quality of life** Total score: -33.6 (p=0.04) Impact on function: -165.2 (p=0.02) Pain, stiffness: NS
							Functional Assessment of Cancer Therapy – General [BL to Wk 6]	**Increased wellbeing** Physical: +3.5 (p=0.03) Social/family, emotional and functional: NS
							Inflammatory markers (TNF-α, IL-1β) [BL to Wk 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Crew, et al. (2010) [USA, AMRO] [17]	Randomized controlled trial	Breast cancer stage I-IIIa hormone receptor positive – aromatase inhibitor induced joint pain	Standardized full body and auricular acupuncture	6 weeks (30 min, twice per week)	Sham acupuncture control (superficial needle insertion at body locations not recognised as true acupoints)	38 (20/18)	Brief Pain Inventory – short form (0-10 scale) [BL to Wk 6]	**Reduced worst pain** Acupuncture: -3.7, Sham: -0.11 Between group: p=0.002 **Reduced pain severity** Acupuncture: -3.34, Sham: +0.10 Between group: p<0.001 **Reduced interference** Acupuncture: -1.99, Sham: -0.02 Between group: p=0.002
							Western Ontario and McMaster Universities Osteoarthritis index [BL to Wk 6]	**Reduced total score** Acupuncture: -96, Sham: +3 Between group: p<0.01 **Reduced pain** Acupuncture: -160, Sham: -14 Between group: p<0.01 **Reduced stiffness** Acupuncture: -69, Sham: +12 Between group: p<0.01 **Reduced functional impact** Acupuncture: -506, Sham: -149 Between group: p=0.01
							Modified Score for the Assessment of Chronic Rheumatoid Affections of the hand (MS-ACRAH) [BL to Wk 6]	**Reduced total score** Acupuncture: -87, Sham:-28 Between group: p<0.01 **Reduced pain** Acupuncture: -59, Sham: -13 Between group: p<0.01 **Reduced stiffness** Acupuncture: -55, Sham: -40 Between group: p=0.01 **Reduced functional impact** Acupuncture: -213, Sham: -31 Between group: p=0.02

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
							Functional Assessment of Cancer Therapy – General [BL to Wk 6]	**Increased physical wellbeing** Acupuncture: +5.7, Sham: -0.7 Between group: p=0.03
Crew, et al. (2012) [USA, AMRO] [52]	Randomized controlled trial	Breast cancer stage I-III hormone receptor negative, completed adjuvant treatment (survivors)	Oral Green tea (Poly E) – Sinecatechins, a combination of four catechin flavonoids from *Camellia sinensis*	6 months (dose escalation: 400mg, 600mg, 800mg, twice per day)	Placebo	34 (26/8)	Dose-limiting toxicity	1 at 400mg (grade III rectal bleeding) 3 at 600mg (grade II weight gain, grade III indigestion and insomnia) 1 at 800mg (grade III liver functional abnormality)
							Maximum tolerated dose	600mg twice daily (BID)
Crew, et al. (2015) [USA, AMRO] [62]	Secondary analysis			Archived blood and urine from women collected in 6 month dose escalation trial			Hepatocyte growth factor (HGF) [BL to Mth 2, 4 and 6]	**Reduced hepatocyte growth factor** Poly E 2mths: 12.7% compared to placebo, 6.3% (p=0.04) 4 Mths and 6 mths (NS)
							Vascular endothethial growth factor (VEGF) [BL to Mth 2, 4 and 6]	NS
							Lipids [BL to Mth 2, 4 and 6]	NS
							Oxidative damage [BL to Mth 2, 4 and 6]	NS
							Inflammatory biomarkers [BL to Mth 2, 4 and 6]	NS
Dhiliwal, et al. (2016) [India, SEARO] [50]	Cohort study	Palliative care patients (requiring homecare services)	Triaging coding system for home-based palliative care based on Edmonton System Assessment Scale (High, Medium, and Low priority). Multi-disciplinary team assessed and managed pain, physical symptoms, and psychosocial issues.	Two visits	Nil	506 (32/105/ 369)	Timing of home visits (time taken in days) [point of referral to first home visit]	High priority: 2.63 ± 0.75 Medium priority: 7.00 ± 1.5 Low priority: 10.54 ± 2.7
							Edmonton System Assessment Scale (ESAS) [initial triaging to first and second home visit]	**Reduced Pain** High: -6 (p<0.05), Medium: -3 (p<0.05) Between group: p<0.001 **Reduced fatigue** High: -4 (p<0.05), Medium: -5 (p<0.05) Between group: p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								Reduced nausea/vomiting High: -3 ($p<0.05$), Medium: -5 ($p<0.05$) Between group: $p<0.001$ **Reduced depression** High: NS, Medium: – 4 ($p<0.05$) Between group: NS **Reduced anxiety** High: -1 ($p<0.05$), Medium: -3 ($p<0.05$) Between group: NS **Reduced sleep loss** High: -2 ($p<0.05$), Medium: NS Between group: $p<0.001$ **Reduced breathlessness** High: -2 ($p<0.05$), Medium: -7 ($p<0.05$) Between group: <0.001 **Reduced appetite loss** High: -3 ($p<0.05$), Medium: -5 ($p<0.05$) Between group: $p<0.05$ **Reduced wellbeing loss** High: -7 ($p<0.05$), Medium: -16 ($p<0.05$) Between group: $p<0.001$
Dobos, et al. (2015) [Germany, EURO] [53]	Cohort study	Cancer survivors (adults)	Mindfulness based stress reduction program alongside relaxation techniques, exercise, cognitive restructuring, dietary interventions, social support, and naturopathic methods of self-regulation and self-care.	11 weeks (6 hours per week with 3 mth follow up)	Nil	117	European Organization for the Research and Treatment of Cancer – Quality of Life [BL to Wk 8 to 3 Mth follow-up]	**Increased quality of life** General health: +8.73 ($p=0.001$) Physical function: +6.3 ($p=0.01$) Role function: +14.07 ($p<0.001$) Emotional function: +13.22 ($p<0.001$) Cognitive function: +7.42 ($p=0.001$)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								Social function: +13.11 (p=0.001) Fatigue: -9.63 (p=0.009) Pain: -9.38 (p=0.33) Insomnia: -17.13 (p<0.001) Constipation: -5.02 (p=0.033) Nausea and vomiting: NS Dyspnea: NS Appetite: NS Diarrhea: NS Financial difficulties: NS
							Hospital and Anxiety Depression Scale [BL to Wk 8 to 3 Mth follow-up]	**Reduced anxiety and depression** Anxiety: -2.31 (p<0.001) Depression: -1.94 (p<0.001)
							Brief multidimenional Life Satisfaction Scale (BMLSS) [BL to Wk 8 to 3 Mth follow-up]	**Increased satisfaction** Life satisfaction: +3.04 (p<0.001) Health satisfaction: +1.95 (p<0.001)
							Freiburg Mindfulness Inventory [BL to Wk 8 to 3 Mth follow-up]	**Increase in mindfulness** +4.29 (p<0.001)
							Adaptive Coping with Disease Questionnaire (AKU) [BL to Wk 8 to 3 Mth follow-up]	**Increased coping** Conscious living: +8.93 (p<0.001) Positive attitudes: +12.21 (p=0.001) Trust in medical help: +5.56 (p=0.007) Trust in divine help: +5.6 (p=0.017) Search for information: +6.77 (p=0.003) Reappraisal of illness: +7.02 (p=0.012)
							Spiritual and religious attitudes in dealing with illness questionnaire [BL to Wk 8 to 3 Mth follow-up]	**Increased** Search: +5.46 (p=0.004) Trust: +5.04 (p=0.031) Reflection: +3.4 (p=0.002)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							Interpretation of Illness Questionnaire IIQ [BL to Wk 8 to 3 Mth follow-up]	**Increased interpretation of value** Something of value: +0.48 (p=0.001) **Reduced interpretation of punishment** Punishment: -0.22 (p=0.005) Challenge: NS Threat/enemy: NS Adverse interruption: NS Weakness: NS Relieving break: NS Call for help: NS
Greenlee, et al. (2012) [USA, AMRO] [55]	Cohort study (analysis of LACE cohort, PMID: 15986109)	Breast cancer survivors (stage I-III)	Antioxidant supplements (vitamin C, vitamin E, zinc, selenium, carotenoid, beta-carotene, lycopene, multivitamins)	Observational study of supplement use (frequency of use in days per week)	Antioxidant supplement non-users	2264	All cause mortality (hazard ratio = HR) [association between use and death]	**Reduced mortality risk** Vitamin E, frequent use: HR 0.75 (p=0.02) Increased mortality risk Combination carotenoids, frequent use: HR 1.63 (p=0.03) Multivitamins, Vitamin C, Beta-carotene, Lycopene, Selenium, Zinc: NS
							Deaths from breast cancer (HR) [association between use and death]	**Increased mortality risk** Combination carotenoids, frequent use: HR 1.93 (p=0.02) Multivitamins, vitamin C, vitamin E, beta-carotene, lycopene, selenium, zinc: NS
							Breast cancer recurrence (HR) [association between use and recurrence]	**Reduced risk of recurrence** Vitamin C, frequent user: HR 0.71 (p=0.01) Vitamin E, frequent use: HR 0.7 (p<0.01) Multivitamins, combination carotenoids, beta-carotene, lycopene, selenium, zinc: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Greenlee, et al. (2013) [USA, AMRO] [56]	Randomized controlled trial	Breast cancer survivors (stage 0-IIIa – Minority groups)	Curves program (IA) (30 min exercise circuit, a high vegetable, low fat, calorie-restricted diet)	12 months (6 mths intervention with 90 min exercise per week, calorie-restriction for 1-2 wks, 6 mths observation)	Wait list control arm (WCA): 6 mth observation and 6 mth curves program	42 (22/20)	Weight loss (% change) [BL to Mth 6, Mth 12]	**Reduced weight** Mth 6: IA, -3.3%; WCA, 1.8% (p=0.04) Mth 12: regained some but not all of weight lost during first 6 months (p=0.02)
							Retainment	90.5% were retained for the full 12 months
Delgado-Cruzata, et al. (2015) [USA, AMRO] [63]	Selected cohort sub-analysis				Nil	24	Anthropometric measures (mean change, %) [BL to Mth 6 and 12]	**Reduced weight** Mth 6: -1.9 (p=0.01), Mth 12: -2.1 (p=0.01) **Reduced waist circumference** Mth 6: -2.7 (p<0.01), Mth 12: -2.7 (p=0.01) **Reduced body fat** Mth 6: -2.4% (p=0.03), Mth 12: unavailable Hip circumference: NS Waist-to-hip ratio: NS
							Plasma insulin and HOMA-IR [BL to Mth 6 and 12]	**Reduced insulin resistance** Mth 12: Insulin, -10.6% (p<0.01) HOMA-IR, -11.4% (p<0.01)
							Adaption of Kaiser Physical Activity Survey [BL to Mth 6 and 12]	**Increased physical activity** Mth 6: +1.1 (p<0.001) Mth 12: +0.7 (p<0.001)
							DNA methylation biomarkers [BL to Mth 6 and 12]	**Increase methylation** Mth 6: +4.2%; Mth 12: +3% (p<0.0001)
							Associations between changes in anthropometric measures, metabolic markers, diet, and physical activity and changes in markers of DNA methylation [BL to Mth 6 and 12]	**Increased diet quality** Weight loss: NS 10% body fat decrease: NS 10% caloric intake: -0.48% (CI:0.10-0.86) Physical activity: NS 10% increase in fruit and vege and protein: +0.85% (CI: 0.12-0.70)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Greenlee, et al. (2013) [USA, AMRO] [18]	Cohort study (open label)	Breast cancer (stage I-III) – aromatase inhibitor associated joint pain	Glucosamine sulfate (1,500mg/day) and chondroitin (1,200mg/day)	24 weeks	Nil	39	Outcome Measure in Rheumatology Clinical Trials and Osteoarthritis Research Society International [BL to Wk 12 and 24]	**Reduced joint symptoms** Wk 24: 46% (18/39) of patients met criteria for improvement
							Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (0/100 scale) [BL to Wk 12 and 24]	**Reduced pain** Wk 12: -9.6 (p=0.03), Wk 24: -10.7 (p=0.02) **Increased function** Wk 12: -10.7 (p=0.01), Wk 24 -13.2 (p<0.01)
							Modified score for Assessment and Quantification of Chronic Rheumatoid Affections of the hands and wrrist (0/100 scale) [BL to Wk 12 and 24]	**Reduced pain** Wk 12: -14.4 (p<0.001), Wk 24: -13.8 (p<0.001) **Reduced stiffness** Wk 12: -11.3 (p=0.03), Wk 24: NS **Increased function** Wk 12: -9.2 (p=0.03), Wk 24: -8.5 (p=0.02)
							Brief Pain Inventory (0/100 scale) [BL to Wk 12 and 24]	**Reduced pain severity** Wk 12 -0.7 (p=0.05), Wk 24: NS **Reduced pain interference** Wk 12: NS, Wk 24: -1.0 (p<0.001) **Reduced worst pain** Wk 12: -0.9 (p=0.02), Wk 24: -1.2 (p=0.02)
Greenlee, et al. (2015) [USA, AMRO] [54]	Randomized controlled trial	Breast cancer survivors (stage 0-III)	Culturally based dietary interventions for Hispanic women *"¡Cocinar Para Su Salud!"* (nine sessions on nutrition, education, cooking classes and food shopping field trips) (24 hours total over 12 weeks)	6 months	Control (written dietary recommendations)	70 (34/36)	Daily targeted fruit and vegetable intake (servings) [BL to Mth 3, Mth 6]	**Increased targeted fruit and vegetable intake** Fruit: Mth 3, 2.0 vs 0.0 (p=0.004) Mth 6, 2.7 vs 0.5 (p=0.002) Vegetables: Mth 3, 1.2 vs -0.2 (p=0.001) Mth 6, 1.8 vs 0.6 (p=0.02)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
Greenlee, et al. (2016) [USA, AMRO] [66]	Secondary analysis						Daily total fruit and vegetable intake (servings) [BL to Mth 3, Mth 6]	**Increased total fruit and vegetable intake** Fruit: Mth 3: 1.1 vs -0.3 (p=0.05) Mth 6: 2.0 vs -0.1 (p=0.005) Vegetables Mth 3: 1.1 vs -0.4 (p=0.004) Mth 6: 1.8 vs 0.2 (p=0.005)
							Daily total caloric intake (kcal) [BL to Mth 3, Mth 6]	**Reduced calorie intake** Mth 3: -672.9 vs -92.4 (p<0.0001) Mth 6: -562.9 vs 61.6 (p<0.001)
							Calories from total fat (%) [BL to Mth 3, Mth 6]	NS
							Anthropometric data [BL to 3 Mths and 6 Mths]	**Reduced waist circumference** Waist circumference Mth 3: -1.6 vs +1.7 (p=0.05); Mth 6: NS Weight, BMI, hip circumference and waist hip ratio (NS)
							Daily targeted fruit and vegetable intake daily (servings) [BL to 12 Mths]	**Maintained increase targeted fruit and vegetable intake** Fruit: +2.3 vs.- 0.1 (p<0.01) Vegetables: 1.6 vs 0.1 (p<0.01)
							Daily total fruit and vegetable intake (servings) [BL to 12 Mths]	**Maintained increase total fruit and vegetable intake** Fruit: +2.0 vs.- 0.4 (p<0.01) Vegetables: 1.6 vs -0.2 (p<0.01)
							Fruit intake (subcategories) [BL to Mth 12]	**Reduced fruit juice intake** Fruit juice excluding citrus: -0.1 vs +0.3 (p=0.05) **Increased citrus fruit intake** Citrus fruit: -0.1 vs -0.2 (p=0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								Fruit, excluding citrus; Avocado and similar; Fried fruits NS
							Vegetable intake (subcategories) [BL to Mth 12]	**Increased dark green vegetables** Dark green +0.5 vs -0.1 ($p<0.01$) Deep yellow; Tomato; White potatoes; Other starchy vegetables; Legumes and Other vegetables NS
							Daily total caloric intake (kcal) [BL to 12 Mths]	NS
							Calories from total fat (%) [BL to 12 Mths]	NS
							Inflammatory markers [BL to 12 Mths]	NS
							Anthropometric data [BL to 12 Mths]	NS
Greenlee, et al. (2016) [USA, AMRO] [19]	Randomized controlled trial (pilot)	Breast cancer (stage I-III, prevention of chemotherapy-induced peripheral neuropathy)	Electroacupuncture (EA) on GB34, St36, LI4, LI10, Huatuojiaji (L3, L5, C5, C7), Bafeng, Baxie (within 2 days of weekly chemotherapy infusion)	12 weeks (weekly)	Sham acupuncture control	63 (31/32)	Brief Pain Inventory – short form [BL to Wk 6, 12, 16]	**Increased pain** Wk 6, Wk 12: NS Wk 16, between group: p=0.03
							Functional Assessment of Cancer Therapy [BL to Wk 6, 12, 16]	NS
							Neuropathic Pain Scale [BL to Wk 6, 12, 16]	**Increased pain** Wk 6, Wk 12: NS Wk 16, between group: p=0.03
Greenlee, et al. (2018) [USA, AMRO] [43]	Uncontrolled trial (feasibility study)	Breast and colorectal cancer survivors, (females with body mass index ⩾25 kg/m^2)	Weight loss intervention via individualized telephone-based behavioral counselling, community-situated physical activity (via fitness centre membership) and dietary modification	12 months (150 mins per week moderate to vigorous exercise, fourteen 40 min counselling sessions, 500 kcal/d decrease in energy intake)	Nil	48	Changes in dietary intake (daily average) [BL to Mth 6 and 12]	**Reduced caloric intake** Breast cancer cohort Mth 6: -555 ($p<0.001$), Mth 12: -502 ($p<0.001$) Colorectal cancer cohort Mth 6: NS, Mth 12: -452 (p=0.002) **Increased total fruits and vegetables** Breast cancer cohort Mth 6: +1.1 (p=0.04)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
								Mth 12: +1.5 (p=0.04) Colorectal cancer cohort: NS Servings of fruit: NS Servings of vegetables: NS Fibre intake: NS
							Changes in physical activity (min, weekly average) [BL to Mth 6 and 12]	**Increased moderate activity** Breast cancer cohort Mth 6: +162 (p=0.003), Mth 12: +178 (p<0.001) Colorectal cancer cohort: NS Hard activity: NS **Increased strength-based activity** Breast cancer cohort Mth 6: +23 (p=0.02), Mth 12: +39 (p=0.02) Colorectal cancer cohort: NS **Increased flexibility-based activity** Breast cancer cohort Mth 6: +7.2 (p=0.03), Mth 12: NS Colorectal cancer cohort: NS **Increased total activity** Breast cancer cohort Mth 6: +199 (p=0.001), Mth 12: +242 (p<0.001) Colorectal cancer cohort Mth 6: +110 (p=0.009), Mth 12: NS
							Anthropometric markers (weight, kg; body mass index, kg/m^2; waist and hip circumference, cm) [BL to Mth 6 and 12]	**Reduced weight (kg)** Breast cancer cohort Mth 6: -5.5 (p<0.01), Mth 12: -7.8 (p<0.01) Colorectal cancer cohort Mth 6: -2.5 (p<0.01), Mth 12: -2.1 (p=0.05) **Reduced body mass index** Breast cancer cohort

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								Mth 6: -1.8 ($p<0.01$), Mth 12: -2.7 ($p<0.01$) Colorectal cancer cohort Mth 6: -0.9 ($p<0.01$), Mth 12: NS **Reduced waist circumference** Breast cancer cohort Mth 6: -5.6 ($p<0.01$), Mth 12: -6.3 ($p<0.01$) Colorectal cancer cohort: NS **Reduced hip circumference** Breast cancer cohort Mth 6: -4 ($p<0.01$), Mth 12: -7.7 ($p<0.01$) Colorectal cancer cohort Mth 6: -2.4 ($p=0.02$), Mth 12: NS
							Metabolic markers (HbA1c, %; fasting glucose, mg/dL; fasting insulin, mIU/L) [BL to Mth 6 and 12]	HbA1c: NS Fasting glucose: NS Fasting insulin: NS
Hershman, et al. (2013) [USA, AMRO] [57]	Randomized controlled trial	Breast cancer survivors (stage 0-III within 6 weeks of completion of initial adjuvant treatment)	Personalised lifestyle recommendations for nutrition and physical activity from a nutritionist (1 hour), and surveillance recommendations from a nurse (1 hour), alongside 'Facing Forward: Life after cancer treatment' (National Cancer Institute printed guide for cancer survivors)	6 months	Facing Forward: Life after cancer treatment' (National Cancer Institute printed guide for cancer survivors)	126 (66/60)	Functional Assessment of Chronic Illness Therapy Satisfaction [BL to Mth 3 and 6]	NS
							Functional Assessment of Cancer Therapy [BL to Mth 3 and 6]	NS
							Impact of Cancer Scale [BL to Mth 3 and 6]	**Reduced existential negative outlook** Mth 3: Intervention -0.2, Control +0.8 Between group: $p=0.04$ Mth 6: NS All other domains: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
							Assessment of Survivor Concerns questionnaire [BL to Mth 3 and 6]	**Reduced health worry** Mth 3: Intervention -0.16, Control +0.31 Between group: p=0.01 Mth 6: NS **Reduced total health worry subscale** Mth 3: Intervention -0.21, Control: +0.18 Between group: p=0.02 Mth 6: NS All other domains: NS
							Center for Epidemiologic Studies Depression measure [BL to Mth 3 and 6]	NS
							Outcomes by ethnicity (Between group: Hispanic/Non-Hispanic) [BL to 3 and 6 mths]	**Associations with Hispanic ethnicity** Increased trust in medical care Mth 3: p=0.03, Mth 6: NS Increased positive self-evaluation Mth 3: p<0.01, Mth 6: p<0.01 Increased existential positive outlook Mth 3: p<0.01, Mth 6: p=0.02 Increased social life interference Mth 3: p=0.02, Mth 6: p<0.01 Increased social value of relationships Mth 3: p<0.01, Mth 6: p=0.04 Increased meaning of cancer Mth 3: p<0.01, Mth 6: p<0.01 Increased health worry Mth 3: p<0.001 Increased higher order positive scales Mth 3: p<0.01, Mth 6: p=0.02

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Greenlee, et al. (2016) [USA, AMRO] [64]	Secondary analysis							Increased physical wellbeing Mth 3: p<0.01, Mth 6: p<0.01 Increased functional wellbeing Mth 3: p<0.01, Mth 6: p<0.01
							Attitudes towards lifestyle behaviors – general health [BL to Mth 3 and 6]	NS
							Attitudes towards lifestyle behaviors – preventing breast cancer recurrence (1-5 scale) [BL to Mth 3 and 6]	**Increased healthy diet attitude** Mth 3, between group: p=0.03 Mth 6, between group: NS Physical activity attitude: NS Dietary supplement attitude: NS
							Knowledge of lifestyle behaviors [BL to Mth 3 and 6]	NS
							Frequency of lifestyle behaviors [BL to Mths 3 and 6]	**Reduced alcohol consumption** Mth 3, between group: p=0.03 Mth 6, between group: NS Red meat consumption: NS Vegetable and fruit consumption: NS Low fat diet: NS Recreational physical activity: NS Tobacco smoking: NS
Hershman, et al. (2013) [USA, AMRO] [20]	Randomized controlled trial	Breast cancer (stage I-III, prevention of chemo-therapy-induced peripheral neuropathy (CIPN))	Acetyl-L-carnitine (ALC)	24 weeks (3000 mg per day)	Placebo	409 (208/201)	Functional Assessment of Cancer Therapy (FACT) – NTX (Taxane neurotoxicity) [BL to Wk 12 and 24]	**Reduced function (increased CIPN)** Wk 12: NS Wk 24: ALC -5.1, Placebo -3.8 Between group: p=0.01

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
Hershman, et al. (2018) [USA, AMRO] [38]	Follow up 2-years post-intervention						FACT – Taxane trial Outcome Index (functional status) [BL to Wk 12 and 24]	**Reduced functional status** Wk 12: NS Wk 24: ALC -4.8, Placebo: -1.4 Between group: p=0.03
							FACT – Fatigue [BL to Wk 12 and 24]	NS
							Adverse events	NS
							FACT-NTX [BL to Wk 36, 52, and 104]	**Reduced function (increased CIPN)** Both groups, over time: p<0.001 Between group average: ALC -1.39 (p=0.01) Between group Wk 12: NS Between group Wk 24: ALC -1.68 (p=0.02) Between group Wk 36: ALC -1.37 (p=0.04) Between group Wk 52: ALC -1.83 (p=0.02) Between group Wk 104: NS
							FACIT Functional Assessment of Chronic Illness Therapy [BL to Wk 36, 52, and 104]	NS
							FACT-Taxane Trial Outcome Index [BL to Wk 36, 52, and 104]	NS
							Predictors of persistence CIPN	**Increased risk** Women <60 Wk 52: p=0.02, Wk 104: p=0.04 Weight (% per 5kg) Wk 52: p=0.001, Wk 104: p=0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Hershman, et al. (2015) [USA, AMRO] [21]	Randomized controlled trial	Breast cancer (stage I-III) – aromatase inhibitor-induced musculoskeletal pain (post-menopausal women)	Omega-3 fatty acid	24 weeks (3.3 g per day: 560mg eicosapentanoic acid plus docosahexaenoic acid in a 40:20 ratio)	Placebo (corn and soybean oil, matched for colour and taste)	249 (122/127)	Brief Pain Inventory – Short form [BL to Wks 6, 12 and 24]	NS
							Western Ontario and McMaster Universities Osteoarthritis Index [BL to Wks 6, 12 and 24]	NS
							Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands [BL to Wks 6, 12 and 24]	NS
							Functional Assessment of Cancer Therapy – Endocrine [BL to Wks 6, 12 and 24]	NS
							Lipid Profile (mg/dL) (Fasting serum) [BL to Wks 6, 12 and 24]	**Reduced triglycerides** Intervention: -22.1, Placebo: -10.3 Between group: p=0.01 Cholesterol: NS C-reactive protein: NS High density lipoprotein: NS Low density lipoprotein: NS
							Adverse events	NS
Shen, et al. (2018) [USA, AMRO] [22]	Secondary analysis	Breast cancer (stage I-III) – aromatase inhibitor-induced musculoskeletal pain (analysis of participants with and without obesity)					Brief Pain Inventory – short form [BL to Wk 6, 12 and 24]	**Reduced worst pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.02 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS **Reduced average pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.002 BMI <30, treatment

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
								compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.005 **Reduced pain interference** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.009 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.01
							Global Ratings of Change questionnaire [BL to Wk 6, 12 and 24]	**Reduced joint stiffness** BMI ⩾30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS Joint pain: NS
							Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands [BL to Wk 6, 12 and 24]	**Reduced pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.04 BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI-treatment group interaction: NS
							Western Ontario and McMaster Universities Osteoarthritis Index [BL to Wk 6, 12 and 24]	**Reduced pain** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.01 BMI <30, treatment compared to placebo

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								Wk 12: NS, Wk 24: NS BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.02
							Lipid Profile (Fasting serum) [BL to Wk 6, 12 and 24]	**Increased high density lipoprotein** BMI ⩾30, treatment compared to placebo Wk 12: NS, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: NS, Wk 24: p=0.002 BMI-treatment group interaction Wk 12: NS, Wk 24: p=0.003 **Reduced triglycerides** BMI ⩾30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI <30, treatment compared to placebo Wk 12: p=0.02, Wk 24: NS BMI-treatment group interaction Wk 12: p=0.01,Wk 24: NS
Hershman, et al. (2018) [USA, AMRO] [23]	Randomized controlled trial	Breast cancer (Stage I-III hormone receptor positive – aromatase inhibitor induced joint pain)	Acupuncture joint specific protocol (Acu)	6 weeks (30-45 min, twice per week)	Sham acupuncture, Waitlist (WL) control	226 (110/59/57)	Brief Pain Inventory – Short Form [BL to Wk 6, Wk 12]	**Reduced worst pain** Wk 6 Acu: -2.05, Sham: -1.07, WL: -0.99 Between group: Sham p=0.01, WL p=0.01 Wk 12 Acu: -2.31, Sham: -1.51, Waitlist: -0.19 Between group: Sham NS, Waitlist p<0.001 **Reduced average pain** Wk 6 Acu: -1.45, Sham: -0.76,

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
								WL: -0.81 Between group: Sham p=0.04, WL p=0.01 Wk 12 Acu: -1.95, Sham: -1.07, WL: -0.62 Between group: Sham p=0.02, WL: p<0.001 **Reduced pain interference** Wk 6 Acu: -1.69, Sham: -0.82, WL: -0.94 Between group: Sham p=0.02, Waitlist NS Wk 12 Acu: -1.8, Sham: -1.45, WL: -0.7 Between group: Sham NS, Waitlist p=0.003 **Reduced pain severity** Wk 6 Acu: -1.5, Sham: -1.00, WL: -0.82 Between group: Sham p=0.05, WL p=0.01 Wk 12 Acu: -1.82, Sham: -1.34, WL: -0.39 Between group: Sham NS, Waitlist p<0.001
Hudson (1991) [USA, AMRO] [49]	Case reports	Cervical cancer (Class IV)	Escharotic treatment to the cervix: bromelain powder applied to the cervix for 15 min followed removal with *Calendula officinalis* succus, *Sanguinaria canadensis* tincture 75% and zinc chloride 90 g/60 ml sterile water 25% applied to cervix for 1 min then removed with *Calendula officinalis* succus, vaginal suppositories containing	9 weeks (Powder, succus, tincture, vaginal suppositories, and douche. Repeated twice weekly for five weeks. Capsules 2 – 6 each daily. Emulsion on tampon were applied each night, then	Nil	7	Pap smear [BL to Wk 10, Mth 3, 6 and 12]	**Reduced pap smear** BL: class IV (7) Wk 10: class I (4), class II (1), class IV (2 – 1 regression of dysplasia on ectocervix to class I) Mth 3: class I continued remission (1-4), regression of endocervix in subject 6 to class II, class II (subject 5), class IV (subject 7 – continue to show regression of dysplasia on ectocervix to complete remission)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
			magnesium, iron, *Hydrastis canadensis*, vitamin A, *Melaleuca alternifolia* volatile oil, *Citrus x aurantium* volatile oil, an*d Thuja occidentalis* volatile oil placed for 24 hours, then vinegar vaginal douche. Oral supplements: vitamin C 6 – 10 g, beta-carotene 120,000–180,000 IU, selenium 400 mcg, *Taraxacum officinal*e root and *Arctium lappa* root, vegan diet, constitutional homeopathic remedy. After treatment: vitamin A emulsion on a tampon (one week) or *Ulmus rubra* suppositories (one week)	rotated again for two more weeks)				Mth 6: complete remission (1-4), class II (subject 5) class IV (subject 6 despite cryosurgery) class I complete remission (subject after conization) Mth 12: remission (1-4), partial relapse class II-III (Subject 5). Complete remission (subjects 6-7)
Jacobs, et al. (2005) [USA AMRO] [58]	Randomized controlled trial	Breast cancer survivors (menopausal symptoms)	Homeopathy – individualized single remedy, or combination medicine	1 year (given every 2 months)	Placebo	83 (26/30/27)	Hot flash frequency, severity [BL to Mths 1, 2, 3, 6, 9 and 12]	NS
							Kupperman menopausal index [BL to Mths 1, 2, 3, 6, 9 and 12]	NS
							Short Form-36 health survey [BL to Mths 1, 2, 3, 6, 9 and 12]	**Increased general health** Between group (compared to placebo) Single: p=0.02, Combination: p=0.03 All other domains: NS
							Follicle-stimulating hormone [BL to Mths 1, 2, 3, 6, 9, 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Jiang et al. (2013) [USA AMRO] [40]	Randomized controlled trial	Colorectal cancer (adults, Normal or High risk)	*Zingiber officinalis (radix)*	28 days(250 mg capsules, total of 2 g per day)	Placebo	50 (normal risk 30 (14/16) increased risk 20 (10/10))	Colonic COX-1 protein level [BL to day 28]	**Risk reduced in high-risk patients** Ginger, -23.8%; Placebo, 18.9%, (p=0.03) Normal risk CRC (NS)
							15-PGDH protein level [BL to day 28]	NS
Raghavendra, et al. (2007) [India, SEARO] [24]	Randomized controlled trial	Breast cancer (stage II and III operable) with chemotherapy-induced nausea and emesis	Yoga: *asana* postures, *pranayama* breathing, meditation and yogic relaxation techniques with imagery (taught by instructor, then practiced from home, plus a supervised session once in 10 days), alongside 4-6 chemotherapy cycles and standard anti-emetic medications	4 chemotherapy cycles (60 min, 6 days per week, during chemotherapy)	Control (psychodynamic supportive – expressive therapy with coping preparation)	62 (28/34)	Nausea frequency and intensity – Morrow Assessment of Nausea and Emesis (MANE) [after 4th cycle of chemotherapy (CT)]	**Reduced nausea** Post-CT frequency Between group: Yoga -0.9 (p=0.01) Post-CT intensity: Between group: Yoga -1.1 (p<0.001) Anticipatory frequency: Between group: Yoga -0.6 (p=0.06) Anticipatory intensity: Between group: Yoga -1.1 (p=0.003)
							Emesis frequency and intensity – MANE [after 4th cycle of CT]	**Reduced emesis** Post-CT frequency: Between group: Yoga -0.6 (p=0.06) Post-CT intensity: Between group: Yoga -0.6 (p=0.05) Anticipatory frequency: NS Anticipatory intensity: Between group: Yoga -0.57 (p=0.04)
							State Trait Anxiety Inventory (STAI) [after 4th cycle of CT]	**Reduced anxiety** Between group: Yoga -8.3 (p<0.001)
							Beck's Depression Inventory [after 4th cycle of CT]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							Distressful treatment-related symptoms (number of) [after 4th cycle of CT]	**Reduced no. symptoms** Between group: Yoga -3.3 (p=0.002)
							Severity of treatment-related symptoms [after 4th cycle of CT]	**Reduced severity** Between group: Yoga -9.7 (p<0.001)
							Symptom distress experienced [after 4th cycle of CT]	**Reduced distress** Between group: Yoga -13.3 (p<0.001)
							Functional Living Index for Cancer – Overall quality of life [after 4th cycle of CT]	**Increased quality of life** Between group: Yoga +30.4 (p<0.001)
							Total chemotherapy toxicity score [after 4th cycle of CT]	**Reduced toxicity** Between group: Yoga -3.8 (p<0.001)
Rao, et al. (2008) [India, SEARO] [27]	Randomized controlled trial	Breast cancer (stage II and III, mood states, quality of life and immune outcomes following surgery)	Integrated yoga program: *pranayama* breathing and yogic relaxation techniques	4 weeks (60 min session pre-operative, 30 min daily at home for 3 weeks post-surgery)	Control (supportive counselling sessions and postoperative exercise rehabilitation) (30 min, daily, at home, for 3 wks)	69 (33/36)	State Trait Anxiety Inventory [BL to Wk 4 post surgery]	**Reduced anxiety state** Yoga: -10.2 (p<0.01); Control: NS Between group: p=0.04 **Reduced anxiety trait** Yoga: -9.4 (p<0.01); Control: NS Between group: p=0.002
							Beck's Depression Inventory [BL to Wk 4 post surgery]	**Reduced depression** Yoga: NS; Control: NS Between group: p=0.008
							Functional Living Index of Cancer [BL to Wk 4 post surgery]	**Increased quality of life** Yoga: NS; Control: NS Between group: p=0.01
							Distressful treatment-related symptoms (number of) [BL to Wk 4 post surgery]	NS
							Severity of treatment-related symptoms [BL to Wk 4 post surgery]	**Reduced severity of symptoms** Yoga: NS; Control: NS Between group: p<0.01

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Rao, et al. (2008) [India, SEARO] [26]		Postoperative outcomes and wound healing					Symptom distress experienced [BL to Wk 4 post surgery]	**Reduced symptom distress** Yoga: -2.9 (p=0.05); Control: NS Between group: p<0.01
							Immune assays – immunoglobulins (serum IgA, IgG, IgM in g/L) [BL to Wk 4 post surgery]	**Increased IgA in control** IgA: Yoga, NS; Control, +0.64 (p=0.005) Between group: p=0.001 IgM: NS IgG: NS
							Immune assays – lymphocytes (CD4+, CD8+, CD56+ counts in %) [BL to Wk 4 post surgery]	**Reduced lymphocytes in control** CD4+:Yoga, NS; Control, -3.5 (p=0.002) Between group: NS CD8+: Yoga, NS; Control, -3.7 (p=0.001) Between group: NS CD56+: Yoga, NS; Control, -4.3 (p=0.001) Between group: p=0.019
							Drain retention following surgery (days) [BL to wk 4]	**Reduced drain retention** Yoga -1.74 (p=0.001)
							Duration of hospital stay (days) [BL to wk 4]	**Reduced duration of hospital stay** Yoga: -1.3 (p=0.003)
							Postoperative duration (days) [BL to wk 4]	NS
							Interval for suture removal (days) [BL to wk 4]	**Reduced interval for suture removal** Yoga: -2.4 (p=0.031)
							Postoperative complications (% yes/no) [BL to wk 4]	NS
							Plasma cytokines (TNF-alpha) [BL to wk 4]	**Reduced plasma cytokines** Yoga: -6.8 (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Rao, et al. (2015) [India, SEARO] [28]		Depression (changes during and post treatment)					Beck Depression Inventory [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced depression** Post-surgery: $p<0.01$ During RT: $p<0.001$ Post-RT: $p<0.001$ During CT: $p<0.001$ Post-CT: $p<0.01$ Positive correlation between depression scores with symptom severity and distress post surgery, mid RT and mid CT ($p<0.001$)
Rao, et al. (2009) [India, SEARO] [25]	Randomized controlled trial	Breast cancer (stage II and III, anxiety related to cancer and associated treatment)	Integrated yoga program: *pranayama* breathing, meditation and yogic relaxation techniques	Full radiotherapy/chemotherapy cycle (60 min, 3 sessions per week during treatment, 4 sessions pre- and post-operatively)	Control (supportive therapy as part of routine care)	38 (18/20)	State Trait Anxiety Inventory [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced anxiety state** Post-surgery: $p<0.05$ During and post-RT: $p<0.05$ During and post-CT: $p<0.001$ **Reduced anxiety trait** Post surgery: $p<0.001$ Post-RT: $p<0.01$ Post-CT: $p<0.001$
							Symptom distress [BL to post-surgery, BL to during RT, post-RT, BL to during CT, post-CT]	**Reduced distress** Post surgery: $p<0.001$ During and post-RT: $p<0.001$ During CT: $p<0.001$ Post-CT: $p<0.05$
Rao, et al. (2017) [India, SEARO] [29]	Randomized controlled trial	Breast cancer (stage II and II, mood states, quality of life and toxicity related to cancer and associated treatment)	Integrated yoga program: *pranayama* breathing, meditation and yogic relaxation techniques (60 min, 4 sessions pre- and post-operatively, 3 sessions per wk during 6-wk radiotherapy, during each chemotherapy session, home practice 6 days per wk)	24 weeks: (60 min, 3 sessions per week during radiotherapy, one session at each chemotherapy treatment, home practice 6 days per week)	Control: supportive counselling sessions (60 min initial session, 15 min session during subsequent hospital visits, additional as required)	69 (33/36)	State Trait Anxiety Inventory [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced anxiety state** Post-surgery: $p=0.04$ Pre-RT: $p=0.005$ During RT: $p=0.009$ Post-RT: $p<0.001$ During CT: $p<0.001$ Post-CT: $p<0.05$
							Beck's Depression Inventory [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced depression** Post-surgery: $p=0.01$ Pre-RT: $p=0.007$ During RT: $p=0.001$ Post-RT: $p<0.001$ Pre-CT: $p=0.02$ During CT: $p<0.001$ Post CT $p<0.002$

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							Subjective symptoms – no. of symptoms, severity, total distress [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Reduced no. symptoms** During RT: p=0.009 During and Post-CT: p=0.003 **Reduced severity** Post-surgery: p<0.001 During RT: p<0.001 During CT: p<0.001 Post-CT: p=0.002 **Reduced distress** Post-surgery: p<0.001 During RT: p<0.001 During CT and Post-CT: p<0.001
							Functional Living Index of Cancer [BL to post-surgery; BL to during radiotherapy (RT), post-RT; BL to during chemotherapy (CT), post-CT]	**Increased quality of life** Between group: Post-surgery: p=0.01 During RT: p<0.001 During CT: p<0.001
							Chemotherapy-related toxicity – WHO toxicity criteria [during CT]	**Reduced overall toxicity** Between group: p=0.01
Rao, et al. (2017) [India, SEARO] [30]	Randomized controlled trial	Breast cancer (stage IV, related sleep quality)	Integrated yoga-based stress-reduction program: didactic lectures, *pranayama* breathing, meditation and yogic relaxation techniques	12 weeks (60 min, at least twice per week)	Control (education and supportive therapy sessions)	91 (45/46)	Pittsburgh Insomnia Rating Scale [Between group – BL to Wk 12]	**Reduced insomnia** Symptom distress: p<0.001 Insomnia parameters: p=0.02 Impact on quality of life: p=0.001 Total score: p=0.001
							Diurnal salivary cortisol [mean of 3 consecutive days at 0600h, 0900h, 2100h, overall mean [BL to Wk 12]	Reduced at 0600h Yoga: p=0.31 Control: NS
							Natural killer cells (NK) [BL to Wk 12]	**Increased NK cells** Between group: p=0.03
							Absolute lymphocyte count [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Schloss, et al. (2015) [Australia, WPRO] [31]	Case study	Breast cancer (chemotherapy-induced peripheral neuropathy (CIPN) and vitamin B12 deficiency)	Vitamin B12 (intramuscular injection) and B-group vitamin complex (oral)	2 months (B12 injection: 1000 mcg, single dose; Oral complex: equivalent 1000 mcg B12, daily)	Nil	1	Blood pathology (vitamins B12, B1, B2, B6, red cell folate) [BL to post-chemo, post-chemo to Mth 2 post-intervention]	**Reduced B12 post-chemotherapy** B12: -78 (deficiency) B1: no change B2: +30 (healthy range) B6: -5 (healthy range) Red cell folate: -86 (healthy range) **Increased B12 post-intervention** B12: +77 (healthy range) B1: +40 (healthy range) B2: -80 (healthy range) B6: +160 (healthy range) Red cell folate: +7 (healthy range)
							CIPN (Patient neurotoxicity questionnaire) [BL to post-chemo, post-chemo to Mth 2 post-intervention]	**Increased CIPN post-chemotherapy** Total neuropathy: +8 (grades 2-3) **Reduced CIPN post-intervention** Total neuropathy: -4 (grade 1)
Schloss, et al. (2017) [Australia, WPRO] [32]	Randomized controlled trial	Newly diagnosed cancer (breast (n=36), lymphoma (n=20) lung n=9), colon (n=4), prostate (n=1) and endometrial (n=1), undergoing chemotherapy)	B-group vitamin complex, initiated 1 week pre-chemotherapy, continued for 12 weeks post-chemotherapy	36 weeks (B1 50 mg, B2 20 mg, B3 100 mg, P5 164 mg, B6 30 mg, folate 500 mcg, B12 500 mcg, biotin 500 mcg, choline 100 mg, inositol 500 mcg)	Placebo	71 (38/33)	Total Neuropathy Score [BL to Wk 12, 24 and 36]	NS
							MD Anderson Brief Pain Inventory [BL to Wk 12, 24 and 36]	NS
							European Organization for the Research and Treatment of Cancer – Quality of Life [BL to Wk 12, 24 and 36]	NS
							Patient Neurotoxicity Questionnaires – sensory, motor or other neuropathy [BL to Wk 12, 24 and 36]	**Reduced sensory neuropathy** Intervention: Wk 2: p=0.03 Wk 24: p=0.005 Wk 36: p=0.021 Placebo: NS Motor and other: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Siegel, et al. (2014) [USA, AMRO] [48]	Uncontrolled trial (phase I)	Hepatocellular carcinoma (advanced, males)	Silybin phosphatidylcholine (1:2 *Silybum marianum* to phosphatidycholine)	12 weeks (escalating from 2 g to 12 g daily, in 3 divided doses)	Nil	3	Plasma silibinin and silibinin glucorinide [BL to Wk 1, 3, 6 and 9, until death]	**Increased silbinin** Wk 1: n=2, Wk 3: n=2 **Increased silibinin glucuronide** Wk 1: n=3, Wk 3: n=1, Wk 6: n=1
							Liver function test [BL to Wk 1, 3, 6 and 9, until death]	**Reduced bilirubin** Wk 3: n=1, Wk 6: n=1, Wk 9: n=1 **Maintained liver enzymes** Wk 1: n=1, Wk 3: n=1, Wk 9: n=1 **Reduced α-fetoprotein** Wk 9: n=1
							Inflammatory biomarkers [BL to Wk 1, 3, 6 and 9, until death]	No clear changes
Torkelson, et al. (2012) [USA, AMRO] [37]	Uncontrolled trial (phase I, dose finding)	Breast cancer (stage I, II or III, pre-radiation therapy)	*Trametes versicolor* (freeze dried mushroom powder)	6 weeks (500 mg per capsule, escalating doses beginning at 3 g, 6 g, or 9 g daily)	Observational group	23 (3/3/3/14)	Common Terminology Criteria for Adverse Events V3.0 [BL to Wk 6]	Total adverse events: 9 Mild: 7, Moderate: 1, Severe: 1 Possibly related to intervention: 3 Mild: 2, Severe: 1 All doses well tolerated
							Immune response (red blood cell parameters, white blood cell parameters, immune-phenotyping peripheral blood mononuclear cells) [BL to post-radiation to Wk 2, 4 and 6]	**Increased lymphocytes** Wk 2: 6 g and 9 g ($p=0.042$) **Increased CD8+ and CD19+ T cells** Wk 6: 9 g ($p<0.001$) **Increased CD19+ B cells** Wk 6: 6 g ($p=0.033$) Red blood cell: NS Absolute white cell count: NS Neutrophils: NS Natural killer cells: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
Vadiraja, et al. (2009) [India, SEARO] [33]	Randomized controlled trial	Breast cancer (stage II-III, adjuvant radiotherapy) symptom management	Integrated yoga program: *asana* postures, *pranayama* breathing, meditation, yogic relaxation (home practice encouraged)	6 weeks (60 min, at least 3 times per week)	Control: brief supportive therapy with education (15 min, 3 – 4 sessions over 6 wks)	88 (44/44)	Hospital Anxiety and Depression Scale [BL to wk 6]	**Reduced anxiety** Yoga: -3.17 ($p<0.001$); Control: -1.23 ($p<0.05$) Between group -3.34 ($p<0.001$) **Reduced depression** Yoga: -3.43 ($p<0.01$); Control: -1.47 ($p<0.01$) Between group: -2.39 ($p<0.01$)
							Perceived Stress Scale [BL to wk 6]	**Reduced stress** Yoga: -5.61 ($p<0.001$); Control: NS Between groups -4.96 ($p<0.001$)
							Diurnal salivary cortisol [collected 6am, 9am, 9pm for 3 consecutive days, BL to Wk 6]	**Reduced salivery cortisol** Between group: 6am, p=0.009; 9am, NS; 9pm, NS Pooled mean: p=0.03
Vadiraja, et al. (2009) [India, SEARO] [36]							Rotterdam Symptom Check list – psychological, physical, activity level [pre- and post-radiotherapy]	**Reduced psychological distress** Yoga: -2.5 ($p<0.001$); Control: NS Between group: $p<0.001$ **Reduced physical distress** Yoga: -3.23 ($p<0.01$); Control: NS Between group: NS Activity level: NS
							European Organization for the Research and Treatment of Cancer – Quality of Life (EORTC QoL C30 questionnaire V1) [pre- and post-radiotherapy]	**Reduced fatigue** Yoga: -12.22 ($p<0.001$); Control: NS Between group: $p=0.001$ **Reduced pain** Yoga: -9.63 ($p<0.01$); Control: NS Between group: $p<0.01$ **Reduced insomnia** Yoga: -23.71 ($p<0.001$);

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Vadiraja,et al. (2009) [India, SEARO] [34]								Control: NS Between group: p=0.04 **Reduced appetite loss** Yoga: NS; Control: +9.89 (p=0.005) Between group: p=0.002 Dyspnea: NS Nausea and vomiting: NS Diarrhea: NS Constipation: NS
							Positive and Negative Affect Schedule [BL to Wk 6]	**Increased positive affect** Yoga: +3.8 (p<0.001); Control: NS Between group: p=0.007 **Reduced negative affect** Yoga: -9.24 (p<0.001); Control: -3.37 (p=0.02) Between group: p<0.001
							European Organization for the Research and Treatment of Cancer – Quality of Life [BL to Wk 6]	**Increased physical function** Yoga: NS; Control: +6.24 (p=0.03) Between group: NS **Increased emotional function** Yoga: +18.67 (p<0.001); Control: +7.65 (p=0.009) Between group: p=0.001 **Increased cognitive function** Yoga: +5.28 (p=0.05); Control: NS Between group: p=0.03 Role function: NS Social function: NS
Vadiraja, et al. (2017) [India, SEARO] [35]	Randomized controlled trial	Breast cancer associated fatigue	Integrated yoga program: *asana* postures, *pranayama* breathing, meditation, yogic relaxation, chanting, self-appraisal and counselling (individual sessions)	12 weeks (at least 2 sessions per week)	Control (supportive counselling sessions)	91 (46/45)	Percieved Stress Scale [BL to Wk 12]	**Reduced stress** Yoga: -32.6% (p=0.01); Control: NS Between group: p<0.001

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
							Fatigue Symptom Inventory – severity, frequency, interference, diurnal variation [BL to Wk 12]	**Reduced severity** Yoga: -61.15% (p<0.001); Control: NS Between group: p<0.001 **Reduced frequency** Yoga: -52.64% (p<0.001); Control: NS Between group: p<0.001 **Reduced interference** Yoga: -72.6% (p<0.001); Control: NS Between group: p<0.001 **Reduced diurnal variation** Yoga: -52.33% (p<0.001); Control: NS Between group: p<0.001
Zick, et al. (2011) [USA, AMRO] [41]	Randomized controlled trial	Colorectal cancer, normal risk (colonic inflammation)	*Zingiber officinalis* (radix) 250 mg capsule (f 5% gingerols)	28 days (8 capsules per day, total 2000 mg daily)	Placebo	33 (16/17)	Eicosanoid levels in normal mucosa, normalized to protein (pg/ug) [BL to Dy 28]	NS
							Eicosanoid levels in normal mucosa, normalized to arachidonic acid (% change) [BL to Dy 28]	**Reduced inflammatory markers** PGE2: Ginger -28.0%, Placebo +26.4% Between group p=0.05 5-HETE: NS 12-HETE: NS 15-HETE: Ginger -15.8%, Placebo +26.7% Between group p=0.04 13-HODE: NS
Zick, et al. (2011) [USA, AMRO] [59]	Randomized controlled trial	Cancer survivors (persistent cancer-related fatigue – adults, >12wks post cancer-related treatment)	Stimulatory acupressure on CV6, GV20 and bilaterally on ST36, SP6, KI13, LI3: High dose (HIS) or Low dose (LIS); Relaxation acupressure (RA) on Yin Tang and bilaterally on Anmian, HT7, LV3, SP6	12 weeks (30 min, HIS and RA: twice per day, LIS: 3 times per week)	Nil	43 (15/14/14)	Brief Fatigue Inventory [BL to Wk 12]	**Reduced Fatigue severity** HIS: -2.2 LIS: -2.7 RA: -4.0 Between group: p=0.027 Adjusted: p=0.013

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Zick, et al. (2015) [USA, AMRO] [42]	Randomized controlled trial	Colorectal cancer, increased risk (colonic inflammation)	*Zingiber officinalis* (radix) 250 mg capsule (standardized 5% gingerols)	28 days (8 capsules per day, total 2000 mg daily)	Placebo	20 (10/10)	Eicosanoid levels in normal mucosa, normalized to protein (pg/ug) [BL to Dy 28]	**Reduced inflammatory markers** Arachidonic acid: Ginger -44%, Placebo +229.4% Between group: p=0.05 **Increased inflammatory markers** Leukotriene B4: Ginger +54.0%, Placebo -4.7% Between group: p=0.04
							Eicosanoid levels in normal mucosa, normalized to arachidonic acid (% change) [BL to Dy 28]	NS
Zick, et al. (2016) [USA, AMRO] [61]	Randomized controlled trial	Breast cancer stage 0-IIII – persistent cancer-related fatigue (female survivors, >12 mths post cancer treatment)	Relaxing acupressure (RA) on Yin Tang and bilaterally on Anmian, HT7, SP6, LV3; Stimulating acupressure (SA) on Du20, CV6 and bilaterally on LI4, ST36, SP6, KI3 (self-administered, 30 min training session)	6 weeks, plus 4 week follow up (3 min each point, daily)	Usual care control	270 (94/90/86)	Brief Fatigue Inventory [BL to Wk 6, Wk 10]	**Reduced fatigue** Wk 6 RA: -2.6, SA: -2.0, Control -1.1 Between group: p<0.001 Wk 10 RA: -2.3, SA: -2.0, Control: -1.0 Between group: p<0.001 BFI score <4 (Wk 6) RA: 66.2%; SA: 60.9%, Control: 31.3% Between group: p<0.001
							Pittsburg Sleep Quality Index [BL to Wk 6, Wk 10]	**Reduced sleep problems** Wk 6 RA: -2.0, SA: -1.4, Control: 0.6 Between group: p<0.05 Wk 10: NS
							Long-Term Quality of Life (LTQL) Instrument – Somatic [BL to Wk 6, Wk 10]	**Increased somatic function** Wk 6 RA: +3.3, SA: +2.0, Control: +0.2 Between group: p<0.05 Wk 10 RA: +3.5, SA: +1.2, Control: +0.6 Between group: p<0.05

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control)	Measure of Outcome	Outcome
Harris, et al. (2017) [USA, AMRO] [65]	Secondary analysis				Nil	19 (9 RA/10 SA)	LTQL – Fitness [BL to Wk 6, Wk 10]	**Increased Fitness** Wk 6 RA: +1.4, SA: +0.5, Control: -0.1 Between group: p<0.05 Wk 10 RA: +2.2, SA: +0.9, Control: +0.4 Between group: p<0.05
							LTQL – Social support [BL to Wk 6, Wk 10]	**Increased social support** Wk 6 RA: +0.1, SA: -0.4, Control: -0.8 Between group: p<0.05 Wk 10 RA: 0.0, SA: -0.8, Control: -0.7 Between group: p<0.05
							LTQL – Spiritual and Philosophical [BL to Wk 6, Wk 10]	NS
							Adverse events	**Non-serious** 6 cases of mild bruising at acupressure sites
							Brief Fatigue Inventory [BL to Wk 6]	**Reduced fatigue** Whole sample: -1.81 (p=0.001) Between group: NS **Reduced sleep problems** Whole sample: -2.17 (p=0.014)
							Neurobiological metabolites: (glutamate + glutamine (Glx) and creatine to total creatine (Cr/tCr) levels [BL to Wk 6]	Changes post-treatment: NS Glx associated with improvements in sleep RA: p=0.02, SA: p=0.01 Cr/rCt associations: NS Associations with fatigue: NS
							Brain functional connectivity (between right posterior insula seed and left dorsolateral prefronal cortex) [BL to Wk 6]	**Reduced functional connectivity** RA: -0.16 **Increased functional connectivity**

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control)	Measure of Outcome	Outcome
								SA: +0.13 Between group: p<0.001 **Reduction associated with increased sleep quality** RA: p=0.03, SA: NS Associations with fatigue: NS
Zick, et al. (2017) [USA, AMRO] [60]	Randomized controlled trial	Breast cancer survivors (stage 0-IIIa), fatigue	Fatigue reduction diet (rich in fruit, vegetables, whole grains, and omega-3 fatty acid-rich foods) with individualized counselling	3 months (counselling weekly for 4 weeks, then every other week)	Control (general health curriculum with individualized counselling matched for time)	30 (15/15)	Brief fatigue Inventory (%) [BL to Mth 3]	**Reduced fatigue** -2.4 vs -0.77, (p=0.001)
							Pittsburgh Sleep Quality Index [BL to Mth 3]	**Increased sleep** -2.5 vs +0.9, (p=0.03)
							Serum fatty acids (%) [BL to Mth 3]	**Improved fatty acid profile** Reduced saturated fatty acid (p=0.04); Increased omega-3 (p<0.01), 3:6 omega (p=0.02)
							Serum nutrient concentrations [BL to Mth 3]	**Increased carotenoid levels** Increase in FRD for total carotenoids (p<0.01), β-cryptoxanthin (p=0.02), lutein (p=0.05), zeaxanthin (p=0.01), lycopene (p=0.05). Control: increase γ-tocopherol (p=0.03)

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18 Cardiovascular Conditions

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HIGHLIGHTS

- Cardiovascular conditions are listed in the top 10 reasons patients seek naturopathic care.
- Naturopaths/NDs work with patients with a history of cardiovascular disease (CVD), to decrease cardiovascular risk, in the treatment and management of hypertension and high cholesterol and in supporting pre- and post-cardiovascular surgery.
- The risk of many cardiovascular conditions is strongly associated with modifiable risk factors – lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, dietary choices and environmental exposures – all which are addressed as part of naturopathic care.
- The individualized and multi-modal naturopathic approach serves as a model of holistic preventive cardiovascular care and management or treatment of cardiovascular conditions.
- 91% of the clinical research investigating naturopathic interventions for cardiovascular conditions indicated a positive outcome in at least one primary or secondary outcome measures.

Globally, cardiovascular disease is the number one leading cause of death with low- and middle-income countries suffering the most, according to the WHO [1]. Cardiovascular diseases can be grouped into generalized cardiovascular disorders (e.g., hypertension, hypotension), diseases of the heart (e.g., congestive heart failure, angina pectoris, myocardial infarct, arrythmia), peripheral vascular diseases (e.g., arteriosclerosis, atherosclerosis, hemorrhoids, intermittent claudication, Raynaud's Syndrome/Disease, stroke, transient ischemic attack, varicose veins) and blood disorders (e.g., anemia, hemorrhage, polycythemia) [2]. Most cardiovascular diseases are considered non-communicable diseases (NCDs) and are strongly correlated with lifestyle and environmental factors. Like other NCDs, there are non-modifiable and modifiable risk factors for cardiovascular diseases. The non-modifiable risk factors include sex, race/ethnicity, age, genetic contribution, and some environmental exposures [3]. Modifiable risk factors have the greatest impact on cardiovascular health and include: lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, tobacco use, dietary choices, stress management, and exposure to environmental pollutants [4, 5].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=11; published in 12 papers) conducted by naturopathic researchers to investigate treatments for cardiovascular disease. This research sampled a total of 1816 participants and was conducted in Australia (n=5), the United States of America (USA) (n=4), India (n=2) and Canada (n=1). The study designs include randomized controlled trials (n=6), uncontrolled trials (n=2), case reports (n=2), a retrospective observational study (n=1) and a secondary analysis (n=1). The studied interventions evaluated either single or combination therapies that involved complex naturopathic interventions which included a combination of lifestyle, dietary (applied nutrition), exercise, herbal, yoga and/or clinical nutrition (n=3), herbal medicines (n=3), clinical nutrition (n=2), massage (n=2), lifestyle recommendations (n=1), acupuncture (n=1), and hydrotherapy (n=1).

The cardiovascular conditions examined include hypertension (n=4), cardiovascular disease risk (n=3), history of cardiovascular disease (n=2), post-surgery cardiovascular support (n=2), venous leg ulcers (n=2) and anemia (n=1). Of all the naturopathic clinical studies examining cardiovascular disease populations, 72.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are

available in *Table 18.1: Clinical research investigating cardiovascular conditions conducted by naturopathic researchers.* This body of naturopathic research on cardiovascular disease is also supported by over 20 observational studies and more than 20 reviews or meta-analysis, as outlined in Chapter 28.

Implications

Naturopathic practice serves as a model of holistic preventive cardiovascular care. Naturopaths/naturopathic doctors support patients with a range of cardiovascular concerns ranging from general cardiovascular risk factors and history of cardiovascular disease, high cholesterol and hypertension to heart failure support and pre- and post-cardiovascular surgery support [6]. Current empirical research indicates that select naturopathic practices, and especially multi-modal naturopathic interventions, hold merit in the treatment of various cardiovascular conditions.

The holistic, patient-centered and preventive approach of naturopathic treatment is conducive to an advanced role in cardiovascular care that aligns with public health aims [7]. Consultation with naturopaths/naturopathic doctors is already known to be associated with positive health behaviours that are known to be important modifiers of cardiovascular disease [8], and the naturopathic community has been able to achieve successful results in NCDs even in the absence of conventional drug treatment [9]. The increasing burden of chronic NCDs associated with modifiable risk factors including unhealthy lifestyles demand identification of novel approaches that can reduce reliance on pharmaceutical management and invasive treatments. Naturopathic practice models offer potential benefit in diverse clinical populations to achieve these aims, both as a stand-alone treatment intervention as well as integrated naturopathic care within standard primary care and cardiology practices. Further attention on developing and evaluating integration of naturopathic practices on clinical outcomes of various cardiovascular diseases is warranted.

Studies investigating specific conditions:

Hypertension

Three naturopathic studies, two from the USA [10, 11] and one from India [12] with a total of 152 participants with hypertension were evaluated. A single-arm, open label study conducted in the USA involving 30 participants with prehypertension or stage 1 hypertension defined as 120-139 mmHg systolic blood pressure and 80-99 mmHg diastolic blood pressure were prescribed a multi-ingredient dietary supplement which containing reserpine-free *Rauwolfia serpentina* [11]. Participants took 1 tablet per day. The 6-month study resulted in a decrease of systolic (-13.6 mmHg, $p<0.0001$) and diastolic (-9.4 mmHg, $p<0.0001$) blood pressure by the end of the study with a concomitant increase in serum potassium at Month 3 (+0.12, $p=0.04$) but not continuing through to Month 6. There were no other significant changes to biological markers. Laboratory results support renal, hepatic and cardiac safety based on the lack of adverse changes in estimated glomerular filtration rate, liver enzymes, and biomarkers of cardiac inflammation and contractility. Nine participants withdrew from the study due to mild-to-moderate adverse effects including nasal congestion, fatigue, and lightheadedness, with some symptoms deemed as pre-existing prior to the study [11].

A randomized controlled trial conducted in India investigating a naturopathic intervention involving manual acupuncture compared with a yogic breathing intervention (i.e., *pranayama*) and resulted in significant reductions in blood pressure [12]. Subjects with hypertension (n=37) (aged 35-60) and no previous exposure to acupuncture were subject to either 20 minutes of breathing or acupuncture. The breathing intervention group completed various breathing patterns led by a naturopathic physician with qualified yoga experience. The acupuncture group received four acupuncture needles that are understood to be anti-hypertensive. A pre- and post- blood pressure measure was taken for all participants. A significant decrease in systolic blood pressure was measured in the breathing intervention group ($p<0.007$), as well as a significant decrease in diastolic blood pressure was observed in the acupuncture group ($p<0.02$), concluding yogic breathing may reduce systolic blood pressure and acupuncture may significantly reduce diastolic blood pressure [12].

A retrospective observation study conducted in the USA investigated the outcome of adjunctive or primary naturopathic care with 85 participants with hypertension over a six month period of time [10]. Analysis of the characteristics of the naturopathic care provided to participants found 76.5% received adjunctive naturopathic care, of which 97.6% received dietary advice, 68.2% exercise advice, 56.5% preventive advice regarding alcohol, 47.1% preventive advice regarding tobacco, 100% were recommended dietary supplementation including omega-3 oil from fish, magnesium, coenzyme Q10, vitamin B6, resveratrol, potassium, herbal medicines including *Rauwolfia serpentina*, *Terminalia arjuna*, *Convolvulus pluricaulis*, *Tribulus terrestris*, *Crataegus oxycanta*, *Allium sativa*, *Taraxacum officinalis*, *Leonurus cardiaca*, *Passiflora incarnata*. The study found that 34.1% ($p=0.038$) had a systolic blood pressure <140mmHg, 26% ($p=0.026$) and a diastolic blood pressure <90mmHg with 29.3% ($p=0.033$) resulting in both systolic and diastolic blood pressure improvement.

Cardiovascular Disease

One uncontrolled trial conducted in Australia and involving 56 patients examined the impact of a natural health product containing omega-3 fatty acids on cardiovascular disease patients or those with cardiovascular risk factors [13]. The study tested omega-3 polyunsaturated fatty acids 260 mg docosahexaenoic acid (DHA) and 120 mg eicosapentaenoic acid (EPA) prescribed at 1 capsule twice a day for 4 weeks and demonstrated a significant reduction in platelet aggregation in healthy volunteers compared to subjects with CVD [13]. A dose of 640 mg/day of omega-3 PUFA was tested in 40 healthy subjects and 16 subjects with CVD. Participants took 520 mg DHA and 120 mg EPA once a day for 4 weeks. Participants with CVD remained on all medications for the study including anti-coagulation and cholesterol lowering medications. Adenosine diphosphate (ADP)-induced and adrenaline-induced platelet aggregation velocity decreased after 4 weeks in healthy volunteers ($p=0.014$, $p=0.013$ respectively). Comparatively, these measurements, ADP ($p=0.776$) and adrenaline ($p=0.476$) aggregation velocity, in subjects with CVD were not significant. However, the velocity of platelet aggregation decreased in response to arachidonic acid ($p=0.009$) and lag time to platelet aggregation increased with thromboxane mimetic U46619 ($p=0.018$) were significant in subjects with CVD.

Clinical finding

Naturopathic care involving lifestyle modification, herbal medicine prescription and a dietary plan over 12-months may significantly reduce 10-year CVD risk and the prevalence of composite metabolic syndrome in patients at high risk for CVD.

A randomized, controlled trial in Canada determined treating patients at high risk for cardiovascular disease with a whole practice naturopathic care intervention reduced event risk over the next ten years [14]. Postal workers (n= 246, aged 25-65) from three different areas of Canada were randomized to a control group or a naturopathic intervention group. Naturopathic intervention included initiation of a lifestyle, botanical, and nutritional care plan at an initial visit plus four additional 30-minute appointments over the course of 1 year. Changes in the naturopathic group included a significant reduction in average 10-year CVD event risk of -3.1 % ($p=0.002$) compared to standard of care. The prevalence of composite metabolic syndrome was also reduced by 16.9% ($p=0.002$).

Post-Cardiac Surgery

Three studies from Australia involving 269 patients examined the impact of naturopathic interventions pre- and post- cardiovascular surgeries [15-17]. One investigated the impact of multi-faceted naturopathic support including lifestyle, dietary recommendations, physical activity, stress management and the prescribing of nutritional supplements (CoQ10, magnesium orotate, alpha-lipoic acid and omega-3) [16], one the effect of lifestyle interventions including light exercise and mental stress reduction [17], and the third measured the effect of massage [15].

Clinical finding

Individualised naturopathic care involving dietary and lifestyle advice, and supplementation with Coenzyme Q10, magnesium, alpha lipoic acid and omega 3 fatty acids for between 3 and 7 days may reduce the need for inotropic drugs in individuals post-cardiac surgery.

In a 2014 study conducted at the Integrative Cardiac Wellness Program run at the Royal Alfred Hospital in Australia, 337 patients underwent whole practice naturopathic interventions post coronary artery bypass graft or cardiac valve surgery [16]. The naturopathic interventions were conducted 3-7 days post-operation and involved individualized, in-hospital naturopathic interventions including dietary and lifestyle advice and supplementation with CoQ10 (225 milligrams, mg), magnesium orotate (1500 mg), alpha lipoic acid (225 mg), and EPA/DHA (900 mg/600 mg). The treatment group receiving naturopathic care demonstrated a reduction in need for inotropic drugs by about 41% compared to control. Between groups there were no significant differences in need of blood transfusion or return to surgery for bleeding, suggesting no short-term increase in anti-coagulation due to EPA/DHA supplementation. This study also assessed the interest of participants to take part in the study and demonstrated 98% of patients would choose to take part in the study if given the option to access these therapies. Forty-eight patients were surveyed 6 months after their surgery and 97% rated the Integrative Cardiac Wellness Program as excellent and 73% claimed the program improved their time at the hospital.

A randomized controlled trial conducted in Australia involving 146 participants with 75 receiving massage treatment post coronary artery bypass graft surgery indicated an amelioration in patient symptoms compared to a usual care control group [15]. Massage therapy

was delivered over two time points post-surgery for 20 minutes per session. The control groups received usual rest care. Assessments were completed via visual analog scales. The massage therapy significantly decreased anxiety ($p<0.0001$), muscular tension ($p=0.002$), and pain ($p=0.001$) while improving relaxation for patients six days post-surgery. Two focus groups completed after the study noted easy implementation of the program to their daily routine [15].

Other Cardiovascular Conditions

Other cardiovascular conditions studied included, heart failure [18, 19], venous leg ulcers [20, 21] and anemia [22]. A prospective triple blind randomized placebo-controlled trial conducted in Australia tested the efficacy of horsechestnut seed extract *(Aesculus hippocastanum)* on venous leg ulcers [20]. Twenty-seven individuals with venous leg ulcerations receiving care from a community nursing service were administered the extract for twelve weeks compared to a control group. Assessment of the wounds at 0, 4, 8, and 12 weeks revealed no significant change between groups with respect to symptoms or healing, but there was a significant reduction in wound sloughing ($p=0.045$) and a reduction in the frequency of dressing changes required at week 12 ($p=0.009$) favoring the treatment group.

Clinical finding

Horsechestnut seed extract *(Aesculus hippocastanum)* may reduce wound sloughing and the frequency of required dressing changes in individuals with venous leg ulcers.

A case report conducted in India on naturopathic treatment for a 33-year-old female with iron deficiency anemia applied different hydrotherapy and massage techniques over a period of 6 days [22]. The patient was not on any medication. Her presenting symptoms included lethargy, dry pruritic skin, weakness, myalgia, and quickness to fatigue. Over the course of treatment, she received a variety of therapies for a total of 90 minutes per day including mud pack, sitz bath, spinal spray, emersion bath, enemas, Swedish massage, massage, and abdominal pack wrap. Infrared ray therapy and low intensity ultrasound were added to treatment to relieve pain. Post treatment her hemoglobin elevated by 8.2 milligrams/ deciliter, mg/dL, from 7.0 mg/dL. No changes were observed in resting blood pressure, pulse rate, or respiratory rate.

Table 18.1 Clinical research investigating cardiovascular conditions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
Bradley, et al. (2011) [USA, AMRO] [10]	Retrospective observational study	Hypertension	Adjunctive or primary naturopathic care over at least 6 months. 76.5% received adjunctive naturopathic care, 97.6% received dietary advice, 68.2% exercise advice, 56.5% preventive advice regarding alcohol, 47.1% preventative advice regarding tobacco, 100% recommended dietary supplementation including omega-3 oil from fish, magnesium, coenzyme Q10, vitamin B6, resveratrol potassium, botanical supplements including *Rauwolfia serpentina, Terminalia arjuna, Convolvulus pluricaulis, Tribulus terrestris, Crataegus monogyna, Allium sativa, Taraxacum officinalis, Leonurus cardiaca, Passiflora foetida.*	Mean duration of care: 13.8 months	Nil	85	Proportion with systolic blood pressure (BP) <140mmHg (%)	**Increased proportion with <140mmHg systolic BP** +34.1 (p=0.038)
							Proportion with diastolic blood pressure <90mmHg (%)	**Increased proportion with <90mmHg diastolic BP** +26 (p=0.026)
							Neither systolic nor diastolic <140/90mmHg	**Reduced proportion with neither systolic nor diastolic BP <140/90mmHg** -35.3 (p=0.033)
							Either systolic or diastolic blood pressure <140/90mmHg	**Increased proportion with either systolic nor diastolic BP <140/90mmHg** +5.9 (p=0.033)
							Both systolic and diastolic blood pressure <140/90mmHg	**Increased proportion with both systolic and diastolic blood pressure <140/90mmHg** +29.3 (p=0.033)
Braun, et al. (2012) [Australia, WPRO] [15]	Randomized controlled trial	Cardiothoracic patients (post-surgery)	Swedish Massage therapy	20-minute massage therapy on the ward on day 3 or 4 and day 5 or 6 of shoulders, neck back scalp, hands, feet or legs	Active control: rest	146 (75/71)	Pain, Visual Analogue Scale [pre- and post-intervention]	**Reduced pain** Massage -1.19 vs placebo -0.32 (p=0.001)
							Anxiety, Visual Analogue Scale [pre- and post-intervention]	**Reduced anxiety** Massage -1.72 vs rest -0.041 (p<0.001)
							Muscular tension, Visual Analogue Scale [pre- and post-intervention]	**Reduced muscular tension** Massage -1.70 vs rest -0.61 (p=0.002)
							Relaxation, Visual Analogue Scale [pre- and post-intervention]	**Increased relaxation** Massage + 2.11 vs rest 0.74 (p<0.0001)
							Satisfaction, Visual Analogue Scale [pre- and post-intervention]	**Increased satisfaction** Massage +0.31 vs rest -0.28 (p=0.016)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
							Heart rate (beats/sec) [pre- and post-intervention]	NS
							Respiratory rate (breaths/min) [pre- and post-intervention]	NS
							Blood pressure (mmHg) [pre- and post-intervention]	NS
Braun, et al. (2014) [Australia, WPRO] [16]	Controlled trial	Cardiothoracic patients (post-surgery coronary artery bypass graft [CABG] and valve surgery)	Integrative cardiac wellness program (ICWP) including (a) nutritional products – CoQ10 225mg, magnesium orotate 1500mg, (R, S)-alpha lipoic acid 225mg, d-Alpha tocopherol 10.08mg, Omega-3 3000mg (EPA 900mg/DHA 600mg) (b) Naturopathic consult on lifestyle, diet, physical activity and emotional wellbeing	4 weeks: (a) three times per day; (b) between day 3 and 6	Historical, usual care	922 total CABG: 585 (176/354) Valve: 337 (161/231)	Atrial fibrillation % [post-surgery]	**Reduced rate** CABG: usual care 36 vs ICWP 26 (p=0.025) Valve surgery NS
							Inotrope use % [post-surgery]	**Reduced inotropic support** CABG: usual care 43 vs ICWP 24 Relative reduction of 42% (p<0.001) Valve surgery: usual care 48 vs ICWP 29 Relative reduction of 40% (p=0.02)
							Low output state % [post-surgery]	**Reduced incidence** CABG: usual care 16 vs ICWP 9 (p=0.025) Valve surgery NS
							Troponin I 24h [post-surgery]	NS
							Length of hospital stay (days) [post-surgery]	NS
							30 Day mortality [post-surgery]	NS
							Blood drainage first 4 h (ml) Total blood loss (ml) [post-surgery]	**Reduced blood loss** CABG: usual care 190 vs ICWP 160 (p=0.01) Valve surgery NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
							Total blood loss (ml) [post-surgery]	**Increased blood loss** CABG: usual care 250 vs ICWP 400 (p<0.0001) Valve surgery NS
							Blood transfusion requirement % [post-surgery]	NS
							Return to theatre due to hemorrhage % [post-surgery]	NS
							Rehabilitation attendance (%) (random sample of 65 patients)	**Increased** IWCP 86 vs usual care 59 (p=0.033)
Leach, et al. (2006) [Australia, WPRO] [20]	Randomized controlled trial	Venous leg ulceration	Horse-chestnut (*Aesculus hippocastanum*) seed extract (HSCE) 375mg HCSE, standardized to 75mg aescin	12 weeks: 1 tablet BID	Placebo	54 (27/27)	Healed leg ulcers (%) [BL to Wk 4, 8, 12]	NS
							Change in wound dimension [BL to Wk 4, 8, 12]	NS
							Symptoms of chronic venous insufficiency [BL to Wk 4, 8, 12]	NS
							Changes in wound topography [BL to Wk 4, 8, 12]	**Reduced wound slough** RM-ANOVA F=2.76, (p=0.045)
							Frequency of dressing changes [BL to Wk 4, 8, 12]	**Reduced dressing frequency** Wk 12 HSCE 1.11 (p=0.009) Placebo 2.48 Between group (p=0.009
							Recurrent episodes [BL to Wk 4, 8, 12]	NS
Leach (2014) [Australia, WPRO] [21]	Case series (prospective)	Venous ulcers (chronic)	Aesculus hippocastanum seed extract 375 mg (standardized to contain 75 mg aescin); and standardized wound dressing protocol	8 – 12 weeks: 1 tablet twice daily	None	2	Factors associated with healing [BL to Wk 4 and 8]	Smaller wound volume, mild-to-moderate chronic venous insufficient, improvement in underlying chronic venous insufficient

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
							Factors associated with non-healing [BL to Wk 4 and 8]	*Pseudomonas aeruginosa* infection of ulcer, larger wound volume, severe chronic venous insufficient that doesn't improve
McEwan, et al. (2013) [Australia, WPRO] [13]	Uncontrolled trial	Cardiovascular disease history (adults)	Omega-3 PUFA (DHA 260mg: EPA 60mg)	4 weeks: 1 capsule BID	Healthy volunteers (HV)	56 (40/16)	Maximum slope – Healthy population [BL to Wk 4]	Adenosine phosphate -5.6 (p=0.014) Adrenaline NS Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS
							Maximum amplitude (%) – Healthy population [BL to Wk 4]	Adenosine phosphate -5.6 (p=0.014) Adrenaline -5.4 (p=0.013) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS
							Lag time (sec) – Healthy population [BL to Wk 4]	Adenosine phosphate NS Adrenaline +10 (p=0.002) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 +5 (p<0.001)
							Maximum slope – CVD population [BL to Wk 4]	Adenosine phosphate NS Adrenaline NS Arachidonic acid +8.4 (p=0.009) Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein NS U46619 NS
							Maximum amplitude (%) – CVD population [BL to Wk 4]	Adenosine phosphate NS Adrenaline NS Arachidonic acid NS Collagen (1.0 ug/mL), NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
								Collagen (1.0 ug/mL), NS C-reactive protein +5.9 (p=0.012) U46619 NS
							Lag time (sec) – CVD population [BL to Wk 4]	Adenosine phosphate NS Adrenaline +10 (p=0.002) Arachidonic acid NS Collagen (1.0 ug/mL) NS Collagen (1.0 ug/mL) NS C-reactive protein, NS U46619 +13 (p=0.0018)
							Platelet activation [BL to Wk 4]	**Reduced platelet activation in healthy population** Healthy: -15%; CVD: NS
Nair, et al. 2015 [India, SEARO] [22]	Case report	Anemia (female)	Mud pack (lower abdomen and eyes), sitz bath/ hip bath, spinal spray, emer-sion bath, enemas, Swedish massage, vibro (talcum) massage, abdominal cold water wrap electrotherapy	90 min sessions, daily, for 6 days	Nil	1	Hemoglobin (mg/dL) [BL to Dy 6]	**Increased hemoglobin** Dy 6: +1.2
							Blood pressure (mmgHg) [BL to Dy 6]	No change
							Pulse rate (beats/min) [BL to Dy 6]	No change
							Respiratory rate (breaths/min) [BL to Dy 6]	No change
Rosenfeldt, et al. (2011) [Australia, WPRO] [17]	Randomized controlled trial	Coronary artery bypass graft or valve elective surgery	Light exercise and mental stress reduction	2 weeks	Usual care	117 (60/57)	Quality of Life	NS
							Length of Stay	NS
							Rate of postoperative atrial fibrillation	NS
Ryan, et al. (2019) [USA, AMRO] [11]	Uncontrolled trial	Hypertension (pre- or stage 1)	1 herbal-mineral caplet per day over a period of 6 months containing *Rosa centifolia, Boerhaavia. diffusa, Dendrogyra cylindrus* (coral powder) (350 mg), magnesium aspartate (200 mg),	6 months: 1 caplet at night before bed	Nil	30	Serum sodium (nmol.\/L) [BL to Mth 6]	NS
							Serum potassium (nmol/L) [BL to Mth 6]	**Increased levels** Mth 3: +0.12 (p=0.04) NS
							Serum calcium (mg/dL) [BL to Mth 6]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
			Convolvulus pluricaulis (100mg), *Terminalia arjuna* (100mg), *Tribulus terrestris* (100mg), low-reserpine *Rauwolfia serpentina* (50 mg), and *Rosa vinca* (25 mg).				Serum magnesium (mg/dL) [BL to Mth 6]	NS
							Aspartate transferase (U/L) [BL to Mth 6]	NS
							Alanine transferase (U/L) [BL to Mth 6]	NS
							e-Glomerular filtration rate (mL/min/BSA) [BL to Mth 6]	NS
							b-type natriuretic peptide (pg/mL) [BL to Mth 6]	NS
							Patient Health Questionnaire-9 [BL to Mth 6]	NS
							Blood pressure (mmHg) [BL to Mth 6]	**Reduced blood pressure** Systolic: -13.6 ($p<0.0001$) Diastolic: -9.4 ($p<0.0001$)
Seely, et al. (2013) [Canada, AMRO] [14]	Randomized controlled trial	Cardiovascular disease	Individualized naturopathic care (NC) and enhanced usual care including diet and lifestyle counseling, nutritional medicine & supplementation, 7 visits over 1 year.	12 months: 7 visits	Usual care	246 (124/122)	10-year CVD risk (Framingham) [BL Wk 25 and 52]	**Reduced risk** NC 7.74%; UC 10.81% Between group -3.07% ($p=0.002$)
							Prevalent metabolic syndrome [BL to Wk 25 and 52]	**Reduced incidence of metabolic syndrome** NC 31.58%; UC 48.48% Between group -16.9% ($p=0.002$)
Sriloy, et al. (2015) [India, SEARO] [12]	Randomized controlled trial (parallel)	Hypertension (acupuncture naïve adults)	Acupuncture, unilateral on left, seeking de qi, on GV20, ST36, LV3, HT7 with manual stimulation to all points except GV20	Single session: 20 min	Slow breathing	37 (18/19)	Blood pressure – systolic (mmHg) [BL to post-test]	**Reduced systolic blood pressure** Acupuncture: NS Slow breathing: $p=0.007$
							Blood pressure – diastolic (mmHg) [BL to post-test]	**Reduced diastolic blood pressure** Acupuncture: $p=0.02$ Slow breathing: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention / Control)	Measure of Outcome	Outcome
Zick, et al. (2008) [USA, AMRO] [18]	Randomized controlled trial	Heart Failure (NYHA functional classes II – III, for ⩾3 months with a left ventricular ejection fraction (LVEF) ⩽40%)	*Crataegus laevigata* (hawthorn) leaf and flower extract WS 1442 (containing 84.3 mg proanthocyanins) (*Crataegus* Special Extract WS1442 (CSE))	6 months: 450 mg twice daily	Placebo	120 (60/60)	Progression to Heart failure [BL to Mth 6]	**Increased progression to heart failure** CSE resulted in 3.9 times risk of progression. Association of increased risk with LVEF <35%
							Six-minute walk distance [BL to Mth 6]	NS
							Peak exercise oxygen consumption [BL to Mth 6]	NS
							Anaerobic threshold [BL to Mth 6]	NS
							Cardiovascular deaths, cardiac events, hospitalizations due to CHF [BL to Mth 6]	NS
							Quality of life, assessed by multiple measures [BL to Mth 6]	NS
Zick et al. (2009) [USA, AMRO] [19]	Secondary analysis						Exercise capacity – 6 min walk test [BL to Mth 6]	NS
							Blood pressure and heart rate [BL to Mth 6]	NS
							Minnesota Living with Heart Failure Questionnaire [BL to Mth 6]	NS
							EuroQoL-5D [BL to Mth 6]	NS
							Left ventricular ejection fraction (LVEF) (%) [BL to Mth 6]	**Increased LVEF** Hawthorn, +0.4 (p=0.004)

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19 Complex Immune Conditions

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HIGHLIGHTS

- The most complex immune conditions treated by naturopaths/NDs include multiple sclerosis, human immunodeficiency virus (HIV) and chronic fatigue syndrome (CFS).
- The naturopathic lens is well suited to complex immune conditions with its focus on complexity, addressing multiple causative factors and physiological systems concurrently.
- Research has demonstrated that Traditional and Complementary Medicine (T&CM) may be particularly useful in managing complex immunological post-infectious sequalae of emerging infections.
- 71.4% of the clinical research investigating naturopathic interventions for complex immune conditions indicated a positive outcome in at least one primary or secondary outcome measures.

Globally complex immune conditions are on the rise and include a diverse range of inflammatory conditions in various organs and/or tissues that are characterized by tissue damage and the formation of immune complexes and are generally associated with progressive onset of extreme debilitating symptoms [1]. Complex immune conditions include autoimmune diseases such as systemic lupus erythematosus and multiple sclerosis (MS), infectious or inflammatory diseases such as glomerulonephritis, vasculitis, and human immunodeficiency virus (HIV), and chronic fatigue syndrome (CFS) [2, 3]. A holistic approach to care is well suited to complex immune conditions that are likely impacted by lifestyle, environmental, social, and other external influences [4].

Overview of Studies

This section is dedicated to highlighting the original clinical research (n=14) conducted by naturopathic researchers investigating treatments for complex immune conditions. This research includes a total of 553 participants and was conducted in the United States of America (USA) (n=9), Canada (n=3), India (n=1) and Australia (n=1). The study designs include randomized control trials (n=6), uncontrolled trials (n=6) and case reports (n=2). The interventions investigated in these studies included clinical nutrition (n=7), herbal medicine (n=2) (of which one prescribed an herbal constituent and one an herbal complex), hydrotherapy (n=2), applied nutrition (n=3), acupuncture (n=2), yoga (n=1), and mindfulness and counselling (n=2). Two studies combined multiple treatments within a complex naturopathic intervention while 12 studies used only one category of intervention.

The complex immune conditions examined in these studies include HIV and Acquired Immune Deficiency Syndrome (AIDS) (n=7), MS (n=5) and CFS (n=2). Of all the naturopathic clinical studies examining complex immune populations, 71.4% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 19.1: Original research on complex immune conditions conducted by naturopathic researchers.*

Implications

The naturopathic philosophy of *holism* and principles *'Treat the Cause'* and *'Treat the Whole Person'* leads naturopaths/naturopathic doctors to view the management of patients with complex immune conditions through a lens of complexity, addressing multiple causative factors and physiological systems concurrently [5] with the aim of improving overall health of patients. The results of the naturopathic research on complex immune conditions suggest several naturopathic interventions warrant consideration in the treatment and management of complex immune conditions. Three of the most common complex immune conditions that naturopaths/naturopathic doctors report treating are MS, HIV and CFS [6]. Due to the chronicity and complexity of many of

these conditions, as well as the absence of recognized cures, patients often have unmet health needs and seek care from naturopaths/naturopathic doctors to reduce symptoms or improve their quality of life [7, 8]. Further research is needed to confirm the preliminary findings of these studies, but the favorable outcome for the available evidence justifies such researcher attention. This may become particularly apparent as many infectious diseases move from acute to chronic management, as has become the case for HIV/AIDS [9]. Research has demonstrated that T&CM may be particularly useful in managing the complex immunological post-infectious sequalae of emerging infectious agents such as SARS, Chikungunya, Ebola [10] and COVID-19 [11-20], so naturopathic intervention may potentially play a role in long-term management of these health issues as well.

Along with the clinical evidence supporting naturopathic intervention in these conditions, the clinical expertise and educational nature of naturopathic care may also be well suited to assisting people living with these conditions to manage their increasing self-directed and practitioner-directed complementary medicine use. For example, a 2006 survey of people living with MS (n=2026) found the majority (84%) use one or more T&CM therapy including dietary changes (59%), nutritional products (46%), herbal medicines (36%), and mind-body therapies (32%) [21]. Another survey of men and women living with HIV/AIDs (n=1675) reported more than 1600 different types of T&CM therapies (1210 T&CM substances, 282 T&CM therapeutic activities and 119 T&CM provider types) used by study participants to treat their HIV/AIDS [22]. With the wide use of T&CM, including naturopathy, in those living with complex immune conditions, it is important that there is more research on the safety and efficacy of naturopathic therapies in this area.

Studies investigating specific conditions:

HIV and AIDS

Seven naturopathic studies conducted in USA (n=3), Canada (n=2) and India (n=1) examined interventions aimed at improving immunity (through increased CD4 count – a receptor on white blood cells that assists in fighting infections and HIV) and addressing symptoms common in patients with HIV [23-29]. The studied interventions primarily examined a single treatment intervention (n=5) [23-26, 29] with two studies including a combination of more than one category of treatment within a naturopathic care framework [27, 28]. Across all studies, the treatments investigated included clinical nutrition (n=2) [23, 27], herbal medicine (n=2) [24, 26], applied nutrition (diet therapy) (n=2) [27, 28], acupuncture (n=2) [27, 29] hydrotherapy (n=2) [25, 28], lifestyle counselling (n=1) [28], and yoga (n=1) [28].

A single-arm clinical trial conducted in the USA investigated a herbal medicine product containing andrographolide (a constituent of *Andrographis paniculata)* in adults with HIV (n=18) and those with no HIV infection (n=13) for 6 weeks [24]. At the end of the intervention period, participants with HIV had a statistically significant increase in serum CD4 levels compared to HIV negative participants (+96.3 cell/mm3; p=0.002) however, this change was not maintained 3 weeks after the intervention finished. Participants also reported a slight increase compared to baseline values in the liver enzyme alanine transferase (ALT) in Week 3 and Week 6 ($p<0.005$), which returned to levels similar to baseline after discontinuation of treatment. No change in HIV-1 RNA levels were reported.

An uncontrolled trial conducted in India investigated a residential naturopathic intervention on CD4 counts of adults (n=96) diagnosed with HIV [28]. The intervention was conducted in a government naturopathic residential sanitorium, and consisted of naturopathic counselling, yoga, hydrotherapy and dietary and lifestyle treatments. The intervention was found to significantly improve CD4 counts in patients with treatment duration of 30 days or longer (p=0.00038), but not for shorter interventions. A case study conducted in Canada reported the outcomes of acupuncture treatment in a naturopathic clinic for a 40-year-old male diagnosed with HIV and Guillain-Barre´ syndrome who presented with symptoms of progressive bilateral paresthesia [27]. The paresthesia prevented bipedal walking that had ascended to the patient's chest and head causing palpitations, partial ophthalmoplegia and impaired taste. The patient refused pharmaceutical therapy and had little improvement with physiotherapy. After weekly 30-minute acupuncture sessions for 6 weeks and then monthly for 10 months (16 treatments in total), the patient experienced sensation in his soles, wrists and ankles, increased energy, more self-confidence, and greater mobility. The patient reported 75% recovery after 3 months, and 90% recovery after one year with resolution of social isolation, anxiety, and low self-esteem.

Multiple Sclerosis

Five naturopathic studies conducted in the USA investigated treatments for MS [30-34]. Two studies investigated nutritional products using a placebo as the control [33, 34], two investigated mindfulness-based stress reduction [30] and the other compared a complex naturopathic intervention to usual care with an MS education protocol [31]. Of the studies using clinical nutrition as an intervention, one focused on the impact of omega-3 fish oil in isolation on MS disease progression [32] and symptoms [33] with a further trial investigating the effects of lipoic acid as a standalone intervention to reduce MS progression [34]. The MS interventions evaluated a diverse range of

outcomes including quality of life, mental health, fatigue, and physical ability.

Clinical finding

Lipoic acid intake may reduce levels of markers for MS disease progression.

A randomized, open-label three-arm trial conducted in the USA examined the effects of different doses of lipoic acid (600mg or 1200mg, twice daily) on individuals with MS (n=37) [34]. The study found each increase of 1ug/mL in serum lipoic acid levels was correlated with a reduction of 11.10 units (p=0.04) in matrix metalloproteinase-9 (MMP-9); a surrogate marker for MS disease progression. Similarly, a dose response relationship was identified between lipoic acid and serum intracellular adhesion molecule-1. An uncontrolled study conducted in the USA involving 10 individuals with relapsing-remittiing MS investigated the clinical outcome associated with 9.6g of omega-3 fatty acid fish oil concentrate (2.9 g EPA with 1.9g DHA) per day for 6 months. Participants' immune cell secretion of matrix metalloproteinase-9 reduced by more than half (-58%) over the study period (p<0.01). A double-blind, placebo-controlled trial involving 39 females with MS and major depressive disorder employed a lower dose of omega-3 fatty acids (5.81g/day; 1.95 g EPA/1.35g DHA) and reported no difference in the Montgomery-Asberg Depression Rating Scale score after 3 months, when compared to placebo [33].

Chronic Fatigue Syndrome

Of the two naturopathic studies that focused on CFS, one was a randomised, controlled trial (n=35) conducted in Canada [35] and the second an uncontrolled, open-labeled trial from Australia [36]. The Canadian trial explored the impact of probiotics on stool aerobes and changes in Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) scales. The study lasted eight weeks and showed increased stool aerobes, anaerobes, *Bifidobacteria* and *Lactobacillus*, but did not show any significant improvements in BDI or BAI [14]. The Australian trial investigated the effects of 16-weeks administration of a multivitamin formula containing ubiquinone (Co-enzyme Q10), alpha-lipoic acid, n-acetyl cysteine, acetyl l-carnitine, and 13 other vitamins and minerals in individuals with CFS (n=10) [36]. Following the intervention period, participants had a statistically significant reduction in fatigue (Chalder Fatigue Scale -9.4; p<0.001) and overall improvement in global symptoms (Clinical Global Impression Scale -0.92, p=0.014) and they reported reduced symptoms of insomnia (Insomnia Severity Index -4.55).

Table 19.1 Original research on complex immune conditions conducted by naturopathic researchers

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control	Measure of Outcome	Outcome
Balfour, et al. (2014) [Canada, AMRO] [23]	Randomized controlled trial	HIV-positive (Antiretroviral treatment naive)	High-dose micronutrient, mineral and antioxidant preparation (K-PAX Ultra®)	8 capsules twice daily over 2 years	100% recommended daily allowance (RDA) preparation of multivitamins and minerals.	127 (not specified)	Baseline micronutrient deficiency	**Low baseline micronutrient levels** Carotene: 24% <1 nmol/L Vitamin D: 67% <75 nmol/L, 24% <40 nmol/L, 3.5% <20 nmol/L Serum folate: 20% <15 nmol/L Vitamin B12: 2.4% <133 pmol/L Lower baseline levels of B12 correlated with lower baseline CD4 count (r = 0.21, p= 0.02)
							Treatment adherence	**Good adherence** Nineteen (15%) withdrew early from the study treatment. Mean treatment adherence was 88%. Subjective adherence was 81% and significantly correlated with pill count (r = 0.29, p <0.001). Adherence was <80% in 75% of participants.
Calabrese, et al. (2000) [USA, AMRO] [24]	Uncontrolled trial	HIV-positive (Adults, >18 yrs)	Andrographolide (from *Andrographis paniculata*)	6 weeks (+ 3 week follow up): 5 or 10 mg/kg three times daily (planned 20 mg/kg three times daily, dose not administered due to adverse effects)	Adults with no human immunodeficiency virus infection	31 (18 HIV+/13 HIV-)	Adverse effects including allergy (including anaphylaxis), fatigue, headache, rash, diarrhea, nausea, abnormal taste, and others [BL to Wk 6]	**High incidence of mild adverse effects** HIV+: 12/13 (92%), one experienced anaphylaxis requiring hospitalization HIV-: 4/5 (80%)
							Serum AST [µL] [BL to Wk 6]	NS
							Serum ALT [µL] [BL to Wk 6]	**Increased ALT** HIV+: Wk 3, +22.3 (p<0.005); Wk 6, +20.6 (p<0.005); Wk 9, NS HIV-: NS
							Serum CD4 count [cell/mm3] [BL to Wk 6]	**Increased CD4 Count** HIV+: Wk 3, NS; Wk 6, 501.1 vs 404.8 (p=0.002); Wk 9, NS HIV-: NS
							HIV-1 RNA [log copies/ml] [BL to Wk 6]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control	Measure of Outcome	Outcome
Corroon, et al. (2018) [USA, AMRO] [25]	Uncontrolled trial	HIV-positive (adults)	Constitutional hydrotherapy	Two treatments per week for 6 weeks (+ 1 week follow-up)	Nil	15	Adverse events [BL to Wk 8]	Nonserious
							Viral load (cp/mL) [BL to Wk 8]	NS
							TNF-alpha (pg/mL) [BL to Wk 8]	NS
							Erythrocyte sedimentation rate (pg/mL) [BL to Wk 8]	NS
							High sensitivity C-reactive protein (mg/L) [BL to Wk 8]	NS
							Blood pressure (mmHg) [BL to Wk 8]	NS
							Body mass index (kg/m2) [BL to Wk 8]	NS
							Mean body fat (%) [BL to Wk 8]	**Reduced body fat** -1.6 ($p < 0.0001$)
							Red blood cell (x106/uL) [BL to Wk 8]	NS
							Hemoglobin (g/dL) [BL to Wk 8]	NS
							Hematocrit (%) [BL to Wk 8]	NS
							CD3 (cells/ul) [BL to Wk 8]	NS
							CD4 (cells/ul) [BL to Wk 8]	NS
							CD8 (cells/ul) [BL to Wk 8]	NS
							Sodium (mmol/L) [BL to Wk 8]	**Reduced sodium** -2.08 ($p = 0.005$)
							Potassium (mmol/L) [BL to Wk 8]	NS
							BUN ratio [BL to Wk 8]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control	Measure of Outcome	Outcome
							Creatinine (mg/dL) [BL to Wk 8]	NS
							Aspartate transferase (IU/L) [BL to Wk 8]	NS
							Alanine transferase (IU/L) [BL to Wk 8]	NS
							Bilirubin (mg/dL) [BL to Wk 8]	NS
							Short Form-36 health survey [BL to Wk 8]	**Increased quality of life** Total: NS Energy/Fatigue: +2.5 (p = 0.03) Physical functioning: NS Pain: NS General health: NS
D'Adamo (1992) [USA, AMRO] [26]	Case series	HIV/Autoimmune deficiency syndrome	*Chelidonium majus* 175 mg, *Sanguinaria canadensis* 5 mg, *Ulmus rubra* 20 mg, 1 – 3 tid; concomitant use of *Glycyrrhiza glabra* solid extract (dose not stated). Capsules of freeze-dried extracts.	Wk 1: 1 capsule TID; Wk 2: 2 capsules TID; 3 capsules there after	None	13 (Anti-retroviral drugs: 8; No anti-retroviral drugs: 5	Lymphadenopathy (count) (n=8) [BL to Wk 3]	**Reduced node size and tenderness** 8/8 had diminished node size and tenderness, 3/6 had total or near total resolution
							Serum CD8 lymphocyte count (n=11) [BL to Wk 3]	**Increased** (mild) in 1/11 (⩽7%) **No change** 5/11 **Mild reduction** 4/11 (⩽7%) **Large reduction** 1/11 (>7%)
							Serum CD4 lymphocyte count (n-11) [BL to Wk 3]	**Increased** 4/11 (⩽7%) **No change** 4/11 **Mild reduction** 3/11 mild decrease
							Self-assessed energy level (n=8) [BL to Wk 3]	**Increased** in 6/8 energy increased **No change** in 2/8
Huff, Cooley and Waller (2008) [Canada, AMRO] [27]	Case Report	Guillain-Barre´ syndrome (40 y.o. male with HIV)	Acupuncture (GB34, GB39, PC6, KI3, BL40, GVD, GV3, BL23); Dietary elimination, weekly B12 injections, calcium-rich multi-nutrient formula	12 months: 6 x 30 min weekly sessions for 7 weeks, then monthly sessions for 10 months (16 treatments)	Nil	1	Perceived Sensation, Coordination, Balance, Mobility [BL to 12 mths]	**Increased sensation** **Increased coordination and balance, and confidence in mobility** **90% recovery of functions**

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ control	Measure of Outcome	Outcome
Joseph, et al. (2015) [India, SEARO] [28]	Uncontrolled trial	HIV-positive	Four study arms based on duration of stay: Group 1: 1 – 7 days; Group 2: 8 – 15 days; Group 3: 16 – 30 days; Group 4: >30 days. Naturopathy treatment: hydrotherapy, dietary advice, raw juices, mud therapy, counselling, sun bath. Yoga treatment: loosening exercises, asanas, pranayama, and deep relaxation techniques.	Antiretroviral medications	Nil	96 (G1: 21/ G2: 28/ G3: 23/ G4: 24)	CD4 count [BL to Discharge]	**Reduced for >30 days treatment** G1: NS G2: NS G3: NS G4: p=0.00038
Louie, et al. (2010) [USA, AMRO] [29]	Uncontrolled trial	HIV-positive	10 months (including 4 months pre-intervention observation): Individualized acupuncture treatment based on tongue and pulse assessments	Usual care	Nil	27	Memorial Symptoms Assessment Scale	NS
							WHO Quality of Life instrument	NS
Menon, et al. (2017) [Australia, WPRO] [36]	Uncontrolled trial	Chronic Fatigue Syndrome	16 weeks: Ubiquinone (Co Q10) 200 mg; alpha lipoic acid 150 mg; N-acetylcysteine (NAC) 2000 mg; Acetyl L-carnitine (ALC) 1000 mg; magnesium (as orotate 500 mg) 64 mg; calcium ascorbate dehydrate (equiv. ascorbic acid 200 mg) 242 mg; cholecalciferol (equiv. Vitamin D3 250 IU); 12.5 ug; a-tocopherol (equiv. natural Vitamin E 50 IU) 60 IU; Retinyl palmitate (equiv. Vitamin A 3000 IU) 900 ug REIU; and vitamin B co-factors: biotin (Vitamin H) (600 ug), thiamine hydrochloride (100 mg), riboflavin (100 mg), nicotinamide (200 mg), calcium pantothenate	Twice daily for 16 weeks	Nil	10	Chalder Fatigue Scale [BL to Wk 16]	**Reduced fatigue** -9.4 ($p < 0.001$).
							Montgomery – Asberg Depression Rating Scale [BL to Wk 16]	NS
							Insomnia Severity Index [BL to Wk 16]	**Improved** -4.55
							Patient Global Impression Scale [BL to Wk 16]	NS
							Clinical Global Impression Scale [BL to Wk 16]	**Improved quality of life** Severity: NS Improvement: -0.92 (p=0.014)
							Work and Social Adjustment Scale [BL to Wk 16]	NS
							Short-Form Health Survey [BL to Wk 16]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control	Measure of Outcome	Outcome
			(100 mg), pyridoxine hydrocholoride (100 mg), folic acid (800 mg), cyanocobalamin (Vitamin B12) (800 mg)					
Rao, et al. (2009) [Canada, AMRO] [35]	Randomized controlled trial	Chronic Fatigue Syndrome	8 weeks: Probiotics (24 billion CFU of *Lactobacillus casei* strain Shirota per day)	Nil	Placebo	35 (19/16)	Stool, total aerobes [BL to Wk 8]	**Increased stool aerobes** Placebo: -0.16; Probiotics: +0.43
							Stool, total anaerobes [BL to Wk 8]	**Increased stool anaerobes** Placebo: +0.03; Probiotics: +0.26
							Stool, bifidobacterial [BL to Wk 8]	**Increased stool bifidobacteria** Placebo: -0.36; Probiotics: +0.66
							Stool, lactobacillus [BL to Wk 8]	**Increased stool lactobacillus** Placebo: +0.15; Probiotics: +1.12
							Beck Depression Inventory [BL to Wk 8]	NS
							Beck Anxiety Inventory [BL to Wk 8]	NS
Senders, et al. (2019) [USA, AMRO] [30]	Randomized controlled trial	Multiple sclerosis	8 weeks: Mindfulness-based stress reduction (Kabat-Zinn); 2 hr classes and one 6-hour retreat	Nil	MS education protocol	67 (33/34)	Feasibility	Practiced on 55% of assigned days, median duration of 38min. No relation to perceived stress, emotional wellbeing or fatigue.
							Perceived Stress Score [BL to Wk 8]	NS
							Short Form-36 [BL to Wk 8]	NS
							Anxiety via Patient Reported Outcomes Measurement Information System (PROMIS) [BL to Wk 8]	NS
							Depression (PROMIS) [BL to Wk 8]	NS
							Fatigue (PROMIS) [BL to Wk 8]	NS
							Pain interference (PROMIS) [BL to Wk 8]	NS
							Connor-Davidson Resilience Scale (CD-RISC) [BL to Wk 8]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control	Measure of Outcome	Outcome
							Paced Auditory Serial Addition Test (PASAT) [BL to Wk 8]	NS
Shinto, et al. (2008) [USA, AMRO] [31]	Randomized controlled trial	Multiple sclerosis	6 months: Naturopathic treatments plus usual care – daily supplementation: multivitamin/mineral without iron, vitamin C, vitamin E, fish oil, and alpha-lipoic acid and intramuscular vitamin B12 once a week. Dietary therapy (4 levels): Level 1 – limit *trans* fatty acids, decrease intake of artificial sweeteners, decrease intake of coffee and alcohol, decrease cigarette use, increase intake of water to 6-8 cups per day; Level 2 (1) plus reduced intake of red meat to two 4-6 oz servings per week; Level 3 (2) plus no refined sugar, no fried foods, no processed/packaged foods, no coffee or alcohol; Level 4 – hypoallergenic diet (Brennamen's food elimination and challenge)	Usual care	MS-focused educational visits with a nurse plus usual care	45 (15/15/15)	Short Form-36	NS
							Modified Fatigue Impact Scale	NS
							Beck Depression inventory	NS
							Stroop test	NS
							Paced Auditory Serial Addition Test-3	NS
							Expanded Disability Status Scale	NS
Shinto, et al. (2009) [USA, AMRO] [32]	Uncontrolled trial	Multiple sclerosis (relapsing-remitting)	6 months (including 3 months wash out): Omega-3 fatty acids in the form of fish oil concentrate (9.6 g/day containing 2.9 g EPA and 1.9g DHA)	6 months (including 3 months wash out)	Nil	10	Immune cell secretion of matrix metalloproteinase-9 [BL to Mth 3]	**Reduced levels** Mth 3: - 58% ($p<0.01$)
							Red blood cell omega-3 fatty acid [BL to Mth 3]	**Increased levels** Increased (x6.3 times) ($p=0.001$)
Shinto, et al. (2016) [USA, AMRO] [33]	Randomized controlled trial	Multiple sclerosis (major depressive disorder)	Omega-3 fatty acids in the form of fish oil at a daily dose of 5.81g (1.95 grams of EPA and 1.35 grams of DHA)	3 months	Placebo	39 (21/18)	Montgomery-Asberg Depression Rating scale	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/control	Measure of Outcome	Outcome
Yadav, et al. (2005) [USA, AMRO] [34]	Randomized controlled trial	Multiple Sclerosis	14 days: Lipoic acid (a) 600mg twice per day; (b) 1200mg once per day; (c) 1200mg twice per day	Nil	Placebo	37 (10/9/9/9)	Serum lipoic acid	**Increased levels** Variable levels across all participants 600mg: 0.2ug/mL 1200mg: 4.8ug/mL 2400mg: not reported Placebo: 0.1 ug/mL Between group: p<0.05
							Matrix metalloproteinase-9 [BL to Dy 14]	**Reduced levels** +1ug/mL serum lipoic acid correlated with -11.10 units of serum matrix metalloproteinase-9 (p=0.04)
							Serum intercellular adhesion molecule-1	**Reduced levels** Dose response with lipoic acid (p=0.03)

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20 Endocrine Conditions

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HIGHLIGHTS

- Endocrine conditions are among the top 10 reasons patients seek naturopathic care.
- The most common endocrine conditions treated by naturopaths/NDs include thyroid conditions, type II diabetes, adrenal-related concerns, insulin resistance and metabolic syndrome.
- The risk of many endocrine conditions is strongly associated with modifiable risk factors – lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, dietary choices and environmental exposures – all which are addressed as part of naturopathic care.
- Naturopaths/NDs are well placed to help in the treatment and prevention of endocrine conditions.
- 91% of the research on naturopathic interventions for endocrine conditions indicated a positive outcome.

The endocrine system is comprised of the hormone-producing glands and the brain structures that direct them, including the adrenals, thyroid, parathyroid, pancreas, ovaries, testes, pituitary gland, pineal gland, and the hypothalamus [1]. Endocrine conditions, such as diabetes, are within the top ten causes of death globally and are recognized as a growing and significant contributor to global disease burden [2]. Risk factors for endocrine pathology are both non-modifiable and modifiable, though the latter are responsible for most endocrine disorders. Non-modifiable risk factors include sex, race/ethnicity, age, genetic contribution, and some environmental exposures [3, 4]. Addressing modifiable risk factors where possible is of the utmost importance in decreasing total body burden, so that possible endocrine disease may be modified or avoided altogether. Modifiable risk factors include lifestyle behaviours, physical activity, sedentariness, obesity, alcohol consumption, tobacco use, dietary choices, stress management, auto-immunity, and environmental exposures [5, 6]. The endocrine system is also particularly sensitive to man-made environmental contaminants that disrupt the synthesis, activity, and receptor availability to endocrine hormones (as a group, called 'xenobiotics') [7].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=23) naturopathic researchers have conducted on endocrinological conditions. This research sampled a total of 2,739 participants and was conducted in India (n=12), the United States of America (USA) (n=8), Australia (n=1) and Argentina (n=1). The study designs include randomized controlled trials (n=10), uncontrolled clinical trials (n=7), case reports (n=5), and a prospective cohort trial (n=1). The studied interventions include clinical nutrition (n=4), yoga (n=4), standard naturopathic care including education and yoga (n=4), multifaceted naturopathic care (n=2), technological feedback education (n=2), acupuncture (n=1), applied nutrition including dietary modifications and/or dietary counselling (n=1), bodywork including Qigong compared to progressive resistance training (n=1), hyperbaric oxygen therapy with stem cell therapy (n=1), hydrotherapy (n=1), and dietary changes plus intermittent hypoxic training (n=1).

All populations studied were adults, and the endocrine conditions examined in these studies include type II diabetes mellitus (Type II DM) (n=14); metabolic syndrome (n=4); hypothyroidism with hyperprolactinemia (n=1); impaired fasting glucose (n=1); pre-diabetes (n=1); and obesity with pre-diabetes (n=1). Of all the naturopathic clinical studies examining endocrine condition populations, 91% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 20.1: Clinical research investigating endocrine conditions conducted by naturopathic researchers.* This body of naturopathic research on endocrine conditions is also supported by 15 observational studies and 17 reviews or meta-analyses conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Endocrine-based pathologies are among the top ten primary health concerns of patients seeking naturopathic care while the endocrine system is considered by naturopaths/naturopathic doctors as the third most important body system in the management of overall patient health [8]. The most common endocrinological conditions for which patients seek naturopathic care include thyroid conditions, type II diabetes, adrenal-related concerns, insulin resistance or metabolic syndrome, and a variety of other endocrine conditions [8]. Naturopathic research indicates that patients with endocrine conditions may benefit from naturopathic care, especially when that care is prescribed as an individualized and complex intervention rather than any one individual component or therapy. Most of the clinical research in this chapter focused on naturopathic interventions in the treatment of Type II DM and have shown a variety of efficacious results.

When taken as a whole, these results suggest that comprehensive naturopathic treatment plans encompassing a variety of treatment modalities may be most effective in treating a complex disease state like Type II DM. This is consistent with how naturopathic medicine is taught and practiced through the lens of the naturopathic philosophy, which views each person – and health – as a composite of multiple dimensions. Naturopathic clinicians are well-placed to help in the treatment and prevention of endocrine pathology due to their specific training in lifestyle counselling and treatment of these risk factors, as well as the underlying recognition of the impact of external influences and environmental factors on an individual's state of health [9, 10].To date, the research on endocrine conditions has primarily focused on dietary, yoga, and acupuncture interventions, with combination treatments having the most notable clinical effects. Given the high prevalence of endocrine disorders worldwide, and the increasing global disease burden associated with these disorders, the results of these studies highlight the potential contribution naturopathic care may make to endocrinological health in the community, as well as underscores the need for further well-powered clinical research.

Studies investigating specific conditions:

Type II Diabetes Mellitus

Seventeen studies, conducted in India (n=9), the USA (n=6), Argentina (n=1) and Australia (n=1) assessed the impact of various interventions in adult Type II DM populations. Yoga (n=5) [11-15] was the most commonly researched intervention, followed by applied nutrition (n=4) [16, 17], Qigong (n=2)[18, 19], herbal medicine (n=3) [20-22] and acupuncture (n=2) [18, 23]. The remaining interventions researched included a single study each on hyperbaric oxygen plus stem cells [24], hydrotherapy as a cold abdominal pack [25], adjunctive naturopathic care [26], and an interactive cell phone feedback system [27].

The five studies conducted in India focusing on type II DM found yoga to be beneficial in reducing need for hypoglycemic medication [11]; reducing fasting plasma glucose (FPG) [13-15]; improvements in blood pressure response to handgrip [15], high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol levels [11]; and reducing BMI, weight, and waist circumference [12]. As part of the Stop Diabetes Movement in India, one uncontrolled clinical trial (n=896) assessing the impact of ten days of daily 90-minute yoga practice sessions (including yoga postures, breathing, cleansing technique, meditation, and 30 minutes of lectures on yoga), resulted in a fasting plasma glucose (FPG) decrease of 11.2 mg/dL ($p<0.001$) [13]. This finding was reproduced in another study (n=15) conducted in India, where just seven days of a similar intervention, the Integrated Approach of Yoga Therapy (IAYT; consisting of yoga postures, regulated breathing, cleansing technique, meditation, and lectures on yoga), resulted in a FPG decrease of 24.4 mg/dL ($p<0.05$) [15]. Additionally, one week of IAYT improved sympathetic nervous system activity, as reflected by an improvement in blood pressure response to sustained handgrip (3.2 mmHg, $p<0.01$).

Two studies conducted in the USA indicated that applied nutrition in the form of naturopathic nutrition education was found to improve diabetes self-care and blood markers associated with diabetes management. Improvements were also noted by a decrease in negative emotions associated with having Type II DM (fear, overwhelm, discouragement) and increased adherence to healthy eating, food selection, attention to dining atmosphere, and feelings of competency in addressing Type II DM [16, 17]. An uncontrolled clinical trial conducted in the USA (n=45) assessed the impact of twelve weeks of a naturopathic whole-foods nutrition education program on multiple blood markers of diabetes in a prediabetic population [17]. The program consisted of weekly, in-person 90-minute workshops that emphasized nutrition education (i.e. the health benefits of a whole foods diet) and imparting practical skills in cooking, food label reading, and grocery shopping; additionally, participants were given a book with recipes and lessons to help guide food choices, and a one-pound bag of the featured grain or legume from the week's lesson, to be used in their home cooking during the next week. Outcomes were measured at twelve weeks, and follow-up assessed at six and twelve months. The primary outcome measure – high sensitivity C-reactive protein (hs-CRP) – decreased at twelve weeks by a mean of 0.7 mg/L

($p<0.05$); a decrease was maintained at both follow-up visits ($p<0.05$). FPG also showed a decrease at 12 weeks (-6 mg/dL, $p<0.01$); further decreases were seen at six months (-11.5 mg/dL, $p<0.001$) and twelve months (-13.9 mg/dL, $p<0.001$). HDL cholesterol – considered a protective marker – initially decreased but increased compared to baseline by the twelve month follow up (6.2 mg/dL, $p<0.01$). Decreases in haemoglobin-A1c (HbA1c) (-0.3 %, $p<0.001$), total cholesterol (-30.3 mg/dL, $p<0.001$), LDL cholesterol (-27.3 mg/dL, $p<0.001$), VLDL cholesterol (-8.5 mg/dL, $p<0.01$), and triglycerides (-37.6 mg/dL, $p<0.01$) from baseline to twelve months were also observed. Fasting plasma insulin increased slightly from baseline to twelve months (+4.9 uIU/mL, ($p<0.001$).

A randomized 3-arm pilot trial conducted in India (n=30) assessed the immediate effect of one of a single dose of three naturopathic interventions on FPG: 250 mL of 30% concentrate bittergourd juice *(L. Momordia charantia)* (n=10); 250 mL of 80% concentrate knol-khol *(L. Brassica oleoracea)*, also known as kohlrabi, (n=10); and 250 mL 88% concentrate ashgourd juice *(Benincasa hispida (Thunb).cogn)* [21]. Plasma samples were collected at 30-, 60-, and 120-minutes post-intervention. Of the three interventions, only the knol-khol gourd juice group showed significant results, with a mean decrease in FPG at 30, 90 and 120-minute time points, with effect seen over time ($p=0.029$, $F=4.739$).

Clinical finding

Qigong may reduce stress and fasting plasma glucose.

Qigong applied in a naturopathic setting was found to be beneficial for decreasing FPG and perceived stress [18, 19]. A randomized controlled trial conducted in the USA (n=20) assessed the impact of twelve weeks of either Yi Ren Medical Qigong (YRMQ, intervention group, n=7), progressive resistance training (PRT, active comparator group, n=5), or usual care (control group, n=8) on perceived stress (Perceived Stress Scale, PSS) and depression (Beck Depression Inventory, BDI); both interventions consisted of one 60-minute instructor-led group session per week, with instructions to practice at least twice per week for 30 minute sessions at home [18]. YRMQ decreased mean PSS score by 29.3% ($p<0.05$), and decreased mean PRT score by 50% ($p<0.03$). All other findings were non-significant. Another similar randomized controlled trial conducted in India (n=32) assessed the impact of twelve weeks of Qigong (intervention group, n=11), usual care (control group, n=10), and PRT (active comparator group, n=11) on FPG, fasting plasma insulin, HbA1c, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [19]. At twelve weeks, mean FPG decreased by -23mg/dL ($p<0.003$), and showed significant between-group differences ($p<0.003$); all other results were non-significant.

A prospective clinical trial conducted in India (n=20) assessed the impact of a single 20-minute application of a cold abdominal pack (CAP; cotton cloth dipped in 15 – 16°C water, wrung out, and placed on the abdomen, then covered with a dry cotton cloth and dry flannel cloth) on random blood glucose (RBG) and several markers of cardiovascular function (systolic and diastolic blood pressure [SBP, DBP; mmHg], pulse rate [PR; beats/minute], pulse pressure [PP; mmHg], mean arterial pressure [MAP; mmHg], rate pressure product [RPP; HRxSBP/100], and double product [Do-P; HRxMAP/100]) [25]. A significant reduction was seen in all outcome measures except DBP and PP. Of note, RBG decreased by -4.8mg/dL ($p=0.011$).

Metabolic Syndrome

Two cross-over randomized controlled trials conducted in the USA assessed micronutrient interventions in adult metabolic syndrome populations. The first study assessed the impact of six months of chromium picolinate supplementation (500 mcg or 1000 mcg dose) compared to placebo in participants (n=59) with impaired fasting glucose, impaired glucose tolerance, or metabolic syndrome (14 participants in the 500mcg group and 19 participants in the 1000 mcg group had a diagnosis of metabolic syndrome) [28]. Primary outcome measures included serum insulin, HOMA-IR, 2-hour plasma glucose, fasting plasma glucose, and 2-hour insulin during oral glucose tolerance testing. Secondary outcome measures included anthropometric measures (body weight, BMI, waist circumference), blood pressure, endothelial function (assessed by flow-mediated dilatation), HbA1c, blood lipid levels, and urinary microalbumin. Results revealed no significant changes in any of the primary or secondary outcome measures within or between groups. The second study assessed the impact of eight weeks of supplementation with two different formulations of encapsulated vegetable and fruit powders in adults with metabolic syndrome (n=64), compared to placebo [29]. The first encapsulated blend consisted of vegetable, fruit, and berry powders, while the second consisted of vegetable and fruit powders only. The primary outcome measure was endothelial function (assessed by flow-mediated dilatation); secondary outcome measures included plasma glucose, serum insulin, serum lipids, and body weight. Results revealed no significant changes in any of the outcome measures within or between groups.

On the other hand, a case study conducted in India of a 40-year old male diagnosed with metabolic syndrome reported highly significant changes in all outcome measures [30]. The intervention consisted of three weeks of naturopathic care (60-90 minutes daily of various intervals of several different hydrotherapeutic interventions, mud therapy, and massage therapy, plus various specific

dietary interventions) and yoga (60 minutes twice daily, consisting of postures, controlled breathing, and relaxation techniques). The patient had reductions from baseline in his weight (-9.5kg), BMI (-3.2 kg/m2), waist circumference (-9cm), insulin intake (-40-0-40), fasting blood glucose (-30mg/dL), postprandial blood glucose (-192 mg/dL), systolic (-38mm/Hg) and diastolic (-10 mm/Hg) blood pressure, and serum lipids (total cholesterol [-41mg/dL], HDL cholesterol [-3mg/dL], LDL cholesterol [-36mg/dL], VLDL cholesterol [-2 mg/dL], triglycerides [-6mg/dL]) at the end of the three week intervention.

Another case study conducted in India involved a 50-year-old male diagnosed with metabolic syndrome (and hypothyroidism) who underwent 'Integrated Yoga Naturopathy', which consisted of a combination of naturopathic detoxification therapies (i.e. therapeutic fasting, calorie restricted diet, hydrotherapy, mud therapy, and manipulative therapies) and yoga therapies (i.e. asanas, pranayama, meditation, relaxation techniques, kriyas, educational lectures, and yoga-based counselling sessions), administered for six weeks [31]. For the duration of the intervention, naturopathic therapies were administered for two hours per day, and yoga therapies for 45 minutes per day. After the 6-week intervention period all outcome measures were improved. These included the patient's lipid profile (total cholesterol [-47mg/dL], HDL cholesterol [+6 mg/dL], LDL cholesterol [-43 mg/dL], triglycerides [-63 mg/dL]), thyroid stimulating hormone (-3.85 mIU/mL), glucose profile (fasting blood glucose [-35 mg/dL], post-prandial blood glucose [-167 mg/dL], HbA1c [-0.7%]), Visual Analog Scale (VAS) for knee (-5) and neck (-4) pain, body weight (-20.3kg), BMI (-7.3 kg/m2), and blood pressure (-22/16 mmHg). As these measures were improved, the patient was able to discontinue use of the following medications: hypertensive (Telmisartan 20 mg), oral hypoglycemics (glimepiride, metformin, and Voglibose 0.03 mg), thyroid (levothyroxine sodium 100 mg), and analgesic (Aceclofenac). After the intervention period, the patient was advised to eat a vegetarian, calorie-restricted diet (1200 Kcal/day); practice juice fasting once per week; and to continue practicing the yoga program. Follow-up done at weeks 14 and 18 showed a continuation of the effects seen at the end of the initial intervention period (week six).

The lack of significant results in the randomized controlled trials assessing interventions for metabolic syndrome highlight the complexity in treating this disease, as it is a diagnosis made of multifactorial pathological processes. This point is underscored by the highly clinically significant changes documented in both case studies, in which the interventions were complex, individualized to the patient and multi-faceted. Further research using a systems approach is warranted in further assessing naturopathic treatments for metabolic syndrome.

Other Endocrine Conditions

Other endocrine conditions studied included pre-diabetic individuals with obesity (n=1) [32] and hypothyroidism with hyperprolactinemia (n=1) [33]. Interventions included applied nutrition with intermittent hypoxic training [32]; and naturopathic care with acupuncture and a yoga-based lifestyle modification program [33].

A case study conducted in India involved a 37-year-old female with hypothyroidism, hyperprolactinemia, and symptoms of hormonal imbalance (hot flashes, irregular periods, vaginal dryness, low libido) who underwent naturopathic care, acupuncture, and a yoga-based lifestyle modification program over an 18-month period [33]. Naturopathic care consisted of dietary recommendations (50-60% of diet as raw fruits, elimination of leafy vegetables), therapeutic fasting (two days per week of only coconut water), water-based therapies (immersion, mud and cold baths, water throat pack and abdominal packs), one hour daily of yoga interventions (alternate nostril breathing, fast abdominal breathing, sun salutations), and 21 daily acupuncture sessions. Outcome measures assessed included weight and serum levels of thyroid stimulating hormone, prolactin, and anti-mullerian hormone. At the end of the 18-month intervention period, the patient was able to discontinue use of her thyroid medication (125 mcg of levothyroxine sodium), and resolved her hormonal imbalance symptoms, reflected in the serum measurements of weight (63kg to 51 kg), TSH (9.2U/ml to 4.6 U/ml), prolactin (34.4 ng/ml to 19.6 ng/ml), and anti-mullerian hormone (0.3 ng/ml to 2.6 ng/ml).

Table 20.1 Clinical research investigating endocrine conditions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Ali, et al. (2011) [USA, AMRO] [28]	Randomized controlled trial (Crossover)	Metabolic syndrome or impaired fasting glucose or impaired glucose tolerance (adults)	Chromium picolinate (capsules, daily)	6 months: 500mcg or 1000mcg	Placebo	59 (500mcg: 30/ 1000mcg: 29)	Serum fasting insulin (IU/l) [BL to Mth 6]	NS
							Homeostasis model assessment of insulin resistance [BL to Mth 6]	NS
							2-hour plasma glucose (mg/dl) [BL to Mth 6]	NS
							Fasting plasma glucose (mg/dl) [BL to Mth 6]	NS
							2-hour insulin during oral glucose tolerance testing (IU/l) [BL to Mth 6]	NS
							Anthropometric measures [BL to Mth 6]	NS
							Blood pressure (mmHg) [BL to Mth 6]	NS
							Endothelial function [BL to Mth 6]	NS
							Hemoglobin A1c (%) [BL to Mth 6]	NS
							Urinary microalbumin (mg/dl) [BL to Mth 6]	NS
							Lipids (mg/dl) [BL to Mth 6]	NS
Ali, et al. (2011) [USA, AMRO] [29]	Randomized controlled trial (Crossover)	Metabolic syndrome (adults)	Encapsulated vegetable and fruit powder concentrate blends. Group 1: vegetable, fruit and berry; Group 2: vegetable and fruit	8 weeks (+ 8 week cross-over washout); 3 capsules twice daily (1 capsule = 750mg)	Placebo	64 (22/ 22/20)	Flow-mediated dilatation of the brachial artery [BL to Wk 8]	NS
							Plasma glucose (mg/dl) [BL to Wk 8]	NS
							Serum insulin (IU/l) [BL to Wk 8]	NS
							Serum lipids (mg/dl) [BL to Wk 8]	NS
							Body weight (kg) [BL to Wk 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Bradley, et al. (2012) [USA, AMRO] [26]	Prospective Cohort	Type II Diabetes (Inadequately controlled)	Adjunctive naturopathic care (ANC)	Number and timing of follow-up visits determined by naturopathic doctor and participant. Study duration was one year.	Usual care cohort	369 (40/329)	Summary of Diabetes Self-Care Activities [BL to Mth 6, Mth 12]	**Increased self-care behaviors** *Mth 6* Glucose checking: improved (p = 0.001) Diet quality: improved (p = 0.001) Physical activity: improved (p = 0.02) *Mth 12* Glucose testing: improved (p=0.003) Physical activity, NS Diet quality, NS
							Personal Health Depression Scale [BL to Mth 6, Mth 12]	**Increased positive mood** *Mth 6* Mood: improved (p = 0.001) % non-depressed: NS *Mth 12* Mood: NS % non-depressed: NS
							Self-Efficacy Scale [BL to Mth 6, Mth 12]	**Increased self-efficacy** *Mth 6* Self- efficacy: improved (p = 0.0001) *Mth 12* Self-efficacy: improved (p=0.002)
							Readiness Index [BL to Mth 6, Mth 12]	**Increased readiness to change lifestyle** *Mth 6* Lifestyle change: improved (p=0.003) Commitment to change: NS *Mth 12* Lifestyle change: improved (p=0.004) Commitment to change: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Perceived Stress Scale [BL to Mth 6, Mth 12]	*Mth 6* Stress: NS *Mth 12* Stress: NS
							Problem Areas in Diabetes [BL to Mth 6, Mth 12]	*Mth 6* Stress: NS *Mth 12* Stress: NS
							Subjective rating of satisfaction with and self-perceived effectiveness of ANC [BL to Mth 6, Mth 12]	NS
							Hemaglobin A1C (%) [BL to Mth 6, Mth 12]	NS
							Total cholesterol: HDL ratio [BL to Mth 6, Mth 12]	NS
							Blood pressure [BL to Mth 6, Mth 12]	NS
							Number of new prescriptions for insulin, sulfonylureas, and metformin per year [BL to Mth 12]	**Increased new prescriptions**
							Number of prescription refills for insulin, sulfonylureas, and metformin per year [BL to Mth 12]	**Increased number of prescriptions** ANC: +1.2 UC: -0.2
							Number of primary care visits, per year [BL to Mth 12]	**Increased primary care visits** ANC: +1.5 UC: +0.0
							Number of nutritionist visits, per year [BL to Mth 12]	No change

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Number of specialist doctor visits, per year [BL to Mth 12]	No change
Das, et al. (2018) [India, SEARO] [25]	Uncontrolled clinical trial	Type 2 Diabetes Mellitus (Adults, male)	Cold abdominal pack (CAP; 15 – 16°C)	20 minutes	Nil	20	Random blood Glucose (mg/dL) [BL to 20 min]	**Reduced blood glucose** -4.8 (p=0.011)
							Systolic Blood Pressure (mmHg) [BL to 20 min]	**Reduced systolic blood pressure** -2.35 (p=0.023)
							Diastolic Blood Pressure (mmHg) [BL to 20 min]	NS
							Pulse Rate (beats/minute) [BL to 20 min]	**Reduced pulse rate** -1.6 (p=0.028)
							Pulse Pressure (mmHg) [BL to 20 min]	NS
							Mean Arterial Pressure (mmHg) [BL to 20 min]	**Reduced levels** -1.55 (p=0.010)
							Rate Pressure Product (units) [BL to 20 min]	**Reduced levels** -3.77 (p=0.006)
							Double Product (units) [BL to 20 min]	**Reduced levels** -2.72 (p=0.003)
Estrada, et al. (2008) [Argentina, AMRO] [24]	Uncontrolled clinical trial	Type II Diabetes Mellitus (Adults)	Hyperbaric oxygen treatment (HBOT) and Intrapancreatic autologous stem cells infusion	HBOT, 10 total 1-hour sessions (1 session per day 5 days prior to injection, and 5 days post-injection), target pressure of 2.3 – 2.5 atmospheres of 100% oxygen.	Nil	25	Fasting plasma glucose (mg/dL) [BL to Mth 3, Mth 6, Mth 9, Mth 12]	**Reduced fasting glucose** Mth 3: -62.2 (p<0.001) Mth 6: -68.5 (p<0.001) Mth 9: -90.6 (p<0.001) Mth 12: -100.4 (p<0.001)
							Hemaglobin A1C (%) [BL to Mth 3, Mth 6, Mth 9, Mth 12]	**Reduced HbA1C** Mth 3: -1.1 (p<0.001) Mth 6: -1.7 (p<0.001) Mth 9: -2.2 (p<0.001) Mth 12: -2.6 (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
				Stem cells harvested from each participant's bone marrow (target of 375 mL bone marrow), for 1 injection into the body and tail of each participant's pancreas.			Basal C-peptide [BL to Mth 3, Mth 6, Mth 9, Mth 12]	**Increased C-peptide** Mth 3: +0.2 (NS) Mth 6: +0.4 (NS) Mth 9: +0.8 ($p<0.04$) Mth 12: +1.8 ($p<0.04$)
							C-Peptide/Glucose ratio [BL to Mth 3, Mth 6, Mth 9, Mth 12]	**Increased ratio** Mth 3: +0.5 (NS) Mth 6: +1.0 ($p<0.003$) Mth 9: +1.4 ($p<0.003$) Mth 12: +2.8 ($p<0.003$)
							Insulin requirements in participants using insulin (n=15) [BL to Mth 3, Mth 6, Mth 9, Mth 12]	**Reduced insulin requirements** Mth 3: -13.2 ($p<0.004$) Mth 6: -20.0 ($p<0.004$) Mth 9: -26.9 ($p<0.004$) Mth 12: -32.3 ($p<0.004$) Discontinued: 27% >50% reduction: 82% (of continued users)
Faridi, et al. (2008) [USA AMRO] [27]	Randomized controlled trial (Pilot)	Type II Diabetes Mellitus (Adults)	NICHE System (an interactive informational feedback system that delivers tailored feedback and reminders through cell phone messaging)	1-day training followed by 3 months of interaction with the NICHE System.	Usual care	30 (15/15)	Adherence by intervention group	Full adherence: 13% 75% adherence: 25%
							HbA1c, trend analysis of glucometer readings between groups [BL to Mth 3]	NS
							Physical activity via pedometers and self-report using the Yale Physical Activity Scale [BL to Mth 3]	NS
							Summary of Diabetes Self-care Activities [BL to Mth 3]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Fuller and Courtney (2016) [Australia WPRO] [32]	Case Report	Obesity and pre-diabetes (Female, 49 years)	Commonwealth Scientific and Industrial Research Organisation (CSIRO) diet and intermittent hypoxic training (IHT) using the GO2® altitude training device	CSIRO diet for 5 weeks, followed by CSIRO diet + IHT (1-hour daily) for 4 weeks	Nil	1	Body weight (kg) [BL to Wk 5, Wk 9]	**Reduced body weight** Wk 5: −2.3 Wk 9: −7.3
							Body mass index (kg/m2) [BL to Wk 5, Wk 9]	**Reduced BMI** Wk 5: −0.9 Wk 9: −2.8
							Waist circumference (cm) [BL to Wk 5, Wk 9]	**Reduced waist circumference** Wk 5: -0.0 Wk 9: −3
							Blood pressure [BL to Wk 5, Wk 9]	**Reduced blood pressure** BL: 118/75 Wk 5: 124/73 Wk 9: 116/72
							Diet quality (3-day food diary) [BL to Wk 9]	**Increased diet quality** Total calorie: -150 % total energy from carbohydrate: -10 % total energy from protein: +7 % total energy from fat: +0.0 Fibre (g): +1.0
							Chalder Fatigue score [Wk 5 to Wk 9]	**Reduced fatigue** Wk 5: 27 ('chronic fatigue') Wk 9: 8, ('normal/healthy')
							Fasting blood glucose (mmol/L) [BL to Wk 5, Wk 9]	**Reduced blood glucose** Wk 5: -0.5 Wk 9: -1.0
							Total cholesterol (mmol/L) [BL to Wk 5, Wk 9]	**Reduced cholesterol** Wk 5: -0.1 Wk 9: -0.6
							High-density lipoprotein (HDL) − cholesterol (mmol/L) [BL to Wk 5, Wk 9]	**Increased HDL cholesterol** Wk 5: +0.7 Wk 9: +0.3

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Low-density lipoprotein (LDL) – cholesterol (mmol/L) [BL to Wk 5, Wk 9]	**Reduced LDL cholesterol** Wk 5: -0.8 Wk 9: -1.0
							Triglycerides (mmol/L) [BL to Wk 5, Wk 9]	**Increased triglycerides** Wk 5: +0.0 Wk 9: +0.2
Gowda, et al. (2017) [India, SEARO] [31]	Case Report	50years old male diagnosed with Metabolic Syndrome and Hypothyroidism	Integrated Yoga Naturopathy (IYN): a combination of naturopathic therapies focused on detoxification (therapeutic fasting, calorie restricted diet, hydrotherapy, mud therapy, and manipulative therapies) and yoga therapies (*asanas*, *pranayama*, meditation, relaxation techniques, kriyas, educational lectures, and yoga-based counseling sessions).	Naturopathy therapies: alternating therapies, 2 hours total per day, for 6 weeks. Yoga therapies: 45 minutes daily, for 6 weeks.	Nil	1	Total cholesterol (mg/dl) [BL to Wk 6]	**Reduced cholesterol** -47
							High-density lipoprotein (HDL) – cholesterol (mg/dl) [BL to Wk 6]	**Increased HDL cholesterol** +6
							Low-density lipoprotein (LDL) – cholesterol (mg/dl) [BL to Wk 6]	**Reduced LDL cholesterol** -43
							Triglycerides (mg/dl) [BL to Wk 6]	**Reduced triglycerides** -63
							Thyroid stimulating hormone (TSH) (mIU/ml) [BL to Wk 6]	**Reduced TSH** -3.85
							Blood glucose [BL to Wk 6]	**Reduced blood glucose** Fasting: -35 Post-prandial: -167
							HbA1c (%) [BL to Wk 6]	**Reduced HbA1C** -0.7
							Pain, Visual Analog Scale [BL to Wk 6]	**Reduced pain** Knee pain: -5 Neck pain: -4
							Body weight (kg) [BL to Wk 6]	**Reduced body weight** -20.3
							Body mass index (kg/m2) [BL to Wk 6]	**Reduced BMI** -7.3
							Blood pressure (mmHg) [BL to Wk 6]	**Reduced blood pressure** -22/16

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Medication use [BL to Wk 6]	**Reduced medication use** All able to be discontinued: anti-hypertensive (Telmisartan 20 mg), oral hypoglycemics (glimepiride, metformin, and Voglibose 0.03 mg), thyroid (levothyroxine sodium 100 mg), and analgesic (Aceclofenac)
Grise, McAllister and Langland (2015) [Australia WPRO] [22]	Case report	Type II Diabetes Mellitus	DB-7: *Gymnema sylvestre* (25% gynemic acids) 75mg; vitamin C 250mg; alanine 250mg; glutamine 100mg; zinc (L-monomethionine) 30mg; chromium 200ug; vanadium 1.5mg. (1 capsule TID). Opti Lipotropic: vitamin B6 30mg; magnesium 75mg; choline 225mg; inositol 600mg; L-methionine 900mg; Dandelion root 300mg; Celandine leaf 150mg; Beet leaf 150mg; Oregon grape root 300mg; Milk Thistle seed 120mg (2 capsules BID). Alpha lipoic acid 300 mg/d, Lypo-spheric vitamin C (1000mg BID). Rauwolfia tincture (10 drops BID-TID). Metformin 500mg (BID). Exercise, motivational interviewing for dietary changes (whole-foods, high-vegetable diet with a maximum of 20 g per day net grain carbohydrates)	10 months	Nil	1	Fasting Glucose (mg/dL) [BL to Mth 7]	**Reduced** 168 to 97 at 7 months
							Glycated hemoglobin – HbAlc (%) [BL to Mth 4, 7 and 10]	**Reduced** 7.7 to 5.0 at 7 months, 4.7 at 10 months
							Liver function tests (IU/L) [BL to Mth 7]	**Reduced** alanine aminotransferase (ALT): 130 – 41 aspartate aminotransferase (AST): 83 – 32
							Fasting Lipid Profile (IU/L) [BL to Mth 7]	**Reduced** total cholesterol: 249 to 296 triglycerides levels: 219 – 76 low density lipoprotein (LDL) levels: 153 -104
							Medication use [BL to Mth 4, 7 and 10]	**Ceased medication use** Metformin and DB-7 at 7 months (no longer meet diagnostic criteria of T2DM)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Kumar, et al. (2017) [India, SEARO] [23]	Randomized controlled trial (Pilot)	Type II Diabetes Mellitus	Acupuncture (TCM style) at CV-12 (4 cun above the center of the umbilicus, depth of 0.5 cun)	Needling at CV-12 for 30 minutes.	Sham placebo (needling at non-acupuncture point 1 cun lateral to CV-12) for 30 minutes	40 (20/20)	Random blood glucose [BL to 30 mins]	**Reduced blood glucose** Acupuncture: -12.25 mg/dL ($p < 0.001$) Sham: NS Between group: NS
McDermott, et al. (2014) [India, SEARO] [12]	Randomized controlled trial (Pilot)	Type II Diabetes Mellitus risk (elevated blood glucose) (Adults)	Yoga sessions were manualized and included stress management education, breathing exercises, loosening exercises, standing, supine, prone, sitting and child poses, as well as a chanting exercise and seated meditation.	1 day (8 hour) group counselling session on healthy lifestyle changes including on diet, physical activity and smoking cessation. Attend at least 3 (up to 6) 75 minute yoga sessions over 8 weeks of the study.	1 day (8 hour) group counseling session on health lifestyle changes including on diet, physical activity and smoking cessation. Asked to do 30 min of walking for 3-6 days/ week for the 8 weeks. Walks were in a park and were monitored.	41 (21/20)	Fasting blood glucose (mmol/L) [BL to Wk 8]	NS
							Post prandial blood glucose [BL to Wk 8]	NS
							Body mass index (kg/m2) [BL to Wk 8]	**Reduced BMI** Yoga: -0.2 (NS) Control: +0.6 (NS) Between group: p=0.05
							Weight (kg) [BL to Wk 8]	**Reduced weight** Yoga: -0.8 (NS) Control: +1.4 (NS) Between group: p=0.02
							Waist circumference (cm) [BL to Wk 8]	**Reduced waist circumference** Yoga: -4.2 ($p<0.05$) Control: +0.7 (NS) Between group: $p<0.01$
							Blood pressure [BL to Wk 8]	NS
							Low-density lipoprotein (LDL) – cholesterol [BL to Wk 8]	NS
							Total cholesterol (mmol/L) [BL to Wk 8]	NS
							Triglycerides (mmol/L) [BL to Wk 8]	NS
							Insulin [BL to Wk 8]	NS
							Insulin resistance [BL to Wk 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Perceived Stress Scale [BL to Wk 8]	NS
Mooventhan and Shetty (2015) [India, SEARO] [30]	Case report	Metabolic syndrome (40 y/o male)	Integrative naturopathic care 60–90 min/day of hydrotherapy, mud therapy, massage therapy and diet therapy including fenugreek powder, and yoga therapies 120-min/ day. 3 weeks treatment.		Thyronorm (levothyroxine sodium) 125 mcg	1	Weight (kg) [BL to Wk 3]	**Reduced weight** -9.5
							Body mass index (kg/m2) [BL to Week 3]	**Reduced BMI** -3.2
							Waist Circumference (cm) [BL to Wk 3]	**Reduced waist circumference** -9
							Insulin Intake (units) [BL to Wk 3]	**Reduced insulin intake** -40-0-40
							Fasting blood glucose (mg/dL) [BL to Wk 3]	**Reduced blood glucose** Fasting: -130 Post-prandial: -192
							Systolic blood pressure (BP) (mmHg) [BL to Wk 3]	**Reduced systolic BP** -38
							Diastolic blood pressure (BP) (mmHg) [BL to Wk 3]	**Reduced diastolic BP** -10
							Serum total triglycerides (mg/dL) [BL to Wk 3]	**Reduced triglycerides** -6
							Serum total Cholesterol (mg/dL) [BL to Wk 3]	**Reduced cholesterol** -41
							High-density lipoprotein (HDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced HDL cholesterol** -3
							Low-density lipoprotein (LDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced LDL cholesterol** -36
							Very-low-density lipoprotein (VLDL) – cholesterol (mg/dL) [BL to Wk 3]	**Reduced VLDL cholesterol** -2

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Nagarathna, et al. (2012) [India, SEARO] [11]	Randomized controlled trial	Type II Diabetes Mellitus (Adults)	Yoga-based Lifestyle modification program (YLSP) tailored to diabetes (Integrated Approach of Yoga for Diabetes (IAYD)	12 weeks of one hour/d, 5 days/week sessions. Then one 2 hour/week session for the next 6 months plus advice for 1 hour daily home practice	Exercise-based Lifestyle modification Program (ELSP)	277 (141/136)	Medication score – Total [BL to Mth 9]	NS
							Medication score – Oral hypoglycemic agents (%) [BL to Mth 9]	**Reduced medication** YLSP: -12.8 ($p<0.001$) ELSP: -3.7 (NS) Between group: $p<0.05$
							Medication score – Lipid lowering drugs [BL to Mth 9]	NS
							Medication score – Antihypertensive drugs [BL to Mth 9]	NS
							Fasting blood glucose [BL to Mth 9]	NS
							HemoglobinA1c [BL to Mth 9]	NS
							Post prandial blood glucose [BL to Mth 9]	NS
							High-density lipoprotein (HDL) – cholesterol (% change) [BL to Mth 9]	**Increased HDL cholesterol** YLSP: +7.0 ($p=0.002$) ELSP: -2.1 (NS) Between group: $p=0.007$
							Low-density lipoprotein (LDL) – cholesterol (% change) [BL to Mth 9]	**Reduced LDL cholesterol** YLSP: -12.3 ($p=0.001$) ELSP: -0.9 (NS) Between group: $p=0.003$
							Triglycerides [BL to Mth 9]	NS
							Total Cholesterol [BL to Mth 9]	NS
							Very-low-density lipoprotein (VLDL) – cholesterol [BL to Mth 9]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Nagasukeerthi, et al. (2017) [India, SEARO] [20]	Randomized controlled trial	Type II Diabetes Mellitus (Adults)	Bell pepper juice *(capsicum annuum var grossum)* plus integrated approach of yoga therapy (IAYT)	100 ml bell pepper juice morning and evening plus daily IAYT sessions throughout the day for four consecutive days	IAYT only	50 (25/25)	Fasting blood glucose [BL to Day 4]	NS
							Post prandial blood glucose (mg/dL) [BL to Day 4]	**Reduced post prandial blood glucose** IAYT+Juice: -68.3 (NS) IAYT only: -42.7 (NS) Between group: p<0.001
							Weight [BL to Day 4]	NS
							BMI [BL to Day 4]	NS
							Systolic blood pressure (mmHg) [BL to Day 4]	**Reduced systolic blood pressure** IAYT+Juice: -14.5 (p<0.05) IAYT only: -6.8 (p<0.05) Between group: p=0.002
							Diastolic blood pressure (mmHg) [BL to Day 4]	NS
							Pulse rate [BL to Day 4]	NS
							Mean arterial pressure [BL to Day 4]	NS
							Pulse pressure (mmHg) [BL to Day 4]	**Reduced pulse pressure** IAYT+Juice: -9.7 (p<0.05) IAYT only: +0.48 (NS) Between group: p=0.003
							Rate pressure product [BL to Day 4]	**Reduced rate pressure product** IAYT+Juice: -19.7 (p<0.05) IAYT only: -8.7 (p<0.05) Between group: p=0.001
							Double product [BL to Day 4]	**Reduced double pressure product** IAYT+Juice: -12.6 (p<0.05) IAYT only: -7.9 (p<0.05) Between group: p=0.03

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Nair (2017) [India, SEARO] [33]	Case report	Hypothyroidism, hyperprolactinemia, hot flushes (Female, 37 years)	Naturopathy and yoga-based lifestyle modification program including dietary recommendations (50-60% of diet as raw fruit + elimination of leafy greens), therapeutic fasting (2 days/week coconut water only), water-based therapies (immersion, mud and cold baths, water throat and abdominal packs), and 1-hour daily yoga interventions (alternate nostril breathing, fast abdominal breathing, sun salutations), and 21 daily acupuncture sessions.	Variable over 18- months	Nil	1	Weight (kg) [BL to Mth 18]	**Reduced weight** -12
							Thyroid stimulating hormone (TSH) (U/ml) [BL to Mth 18]	**Reduced TSH** -4.6
							Prolactin (ng/ml) [BL to Mth 18]	**Reduced prolactin** -15.1
							Anti-mullerian hormone (AMG) (ng/ml) [BL to Mth 18]	**Increased AMH** +2.3
							Thyroxine use [BL to Mth 18]	**Reduced thyroxine use** Discontinued (from 125 mcg per day)
Oberg, et al. (2011) [USA, AMRO] [16]	Uncontrolled trial (pilot)	Type II Diabetes Mellitus (Adults)	Nutrition program delivered as a combination of one-on-one naturopathic physician-delivered dietary counselling and bi-weekly educational sessions for the entire cohort conducted following potluck-style dinners.	Total of 10 hours combined one-on-one (4 30-minute sessions) plus group education (4 90 minute sessions) spread out over 12 week program.	nil	15 enrolled, 12 analysed per protocol	Hemoglobin A1c (HbA1C) (%) [BL to Wk 12]	**Reduced HbA1C** -0.4%, p=0.02
							Serum lipid profile [BL to Wk 12]	NS
							Blood pressure [BL to Wk 12]	NS
							Body Mass Index [BL to Wk 12]	NS
							Summary of Diabetes Self-Care Activities [BL to Wk 12]	**Increased diabetes self-care behavior** Healthy eating pattern (days in last week): +1.8 (p=0.05) Healthy eating pattern (days per week in last month): +1.2 (p=0.02) >5 fruits/vegetables per day (days in last week): +1.3 (p=0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Physical activity (days in last week): +3.4 (p=0.02) Blood glucose checking (% of time): +38% (p=0.05) Checked blood sugar as recommended (days in last week): +3.0 (p=0.04)
							Problem Areas in Diabetes [BL to Wk 12]	**Reduced emotional issues associated with diabetes** Feeling scared about living with diabetes: -1.8 (p=0.006) Feeling overwhelmed by diabetes: -1.9 (p=0.03) Feeling discouraged about diabetes treatment plan: NS Composite score: -18.9% (p=0.05)
							Three-day diary [BL to Week 12]	**Increased healthy eating** Adherence to healthy eating increased (p=0.05)
							Perceptions about Nutritional Counseling [BL to Wk 12]	**Reduced confidence in following dietary guidelines** Average daily carbohydrate intake: NS Attention to type of dietary fat consumed: From 'Seldom' to 'Often' (p=0.04) Know how to follow dietary guidelines: From 'Definitely no' to 'Yes' (p=0.02) Feel in control of my diabetes: From 'Definitely no' to 'Yes' (p=0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Seven Eating Styles Questionnaire [BL to Wk 12]	**Reduced negative eating behaviors** Emotional eating: -0.7 (p=0.02) Food fretting: NS Selecting fast food/fresh food: -0.8 (p=0.05) Attention to sensory/spiritual dimensions of food: -1.2 (p<0.01) Task snacking: NS Attention to dining atmosphere: -0.6 (p=0.01) S Attention to positive social settings: NS Integrated eating score: -3.7 (p=0.03)
Putiri, et al. (2012) [USA, AMRO] [18]	Randomized controlled trial	Type II Diabetes Mellitus (Adults)	Group 1: Yi Ren Medical Qigong (YRMQ) (plus oral diabetes medication), Group 2: Progressive resistance training (PRT) (plus oral diabetes medication)	60 min YRMQ or PRT group session once/ week plus instructions for 30 min at-home sessions at least twice/week for 12 weeks	Usual care (UC; oral diabetes medication)	20 (7/5/8)	Perceived Stress Scale [BL to Wk 12]	**Reduced stress** YRMQ: -29.3%, (p<0.05) PRT: NS UC: NS
							Beck Depression Inventory [BL to Wk 12]	**Reduced depression** YRMQ: NS PRT: -50% (p<0.03) UC: NS
Selvakumar, et al. (2017) [India, SEARO] [21]	Randomized controlled trial (pilot)	Type II Diabetes Mellitus (Adults)	Group 1: 250 ml bittergourd juice (30% concentrate) Group 2: 250 ml Knol-khol (80% concentrate) Group 3: 250 ml ashgourd juice (88% concentrate)	Single dose, morning oral administration	Nil	30 (10/10/ 10)	Fasting plasma glucose [BL to 30 min, 60 min, 90 min and 120 min]	**Reduced blood glucose** Bittergourd: NS Knol-khol: Reduced at 30, 90 and 120 min time points with effect seen over time (p=0.029, F=4.739). Ashgourd: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Sun, et al. (2010) [USA, AMRO] [19]	Randomized controlled trial	Type II Diabetes Mellitus (Adults)	Group 1: Qigong (plus oral diabetes medication) Group 2: progressive resistance training (PRT) (plus oral diabetes medication)	One hour Qigong or PRT sessions once/ week plus instructions for 30min at home sessions/week for 12 weeks	Usual care (oral diabetes medication)	32 (11/11/ 10)	Fasting plasma glucose [BL to Wk 12]	**Reduced blood glucose** Qigong: -23mg/dl (p=0.003) PRT: NS UC: NS Between group: p<0.003
							Fasting plasma Insulin [BL to Wk 12]	NS
							Hemoglobin A1c [BL to Wk 12]	NS
							Homeostasis model assessment of insulin resistance (HOMA-IR) [BL to Wk 12]	NS
Tippens, et al. (2019) [USA, AMRO] [17]	Uncontrolled clinical trial	Prediabetes (adults)	Naturopathic whole-foods nutrition education	12 weeks	Nil	45	High sensitivity c-reactive protein (mg/L) [BL to Wk 12, Mth 6, Mth 12]	**Reduced HsC-RP** Wk 12: -0.7 (p<0.05) Mth 6: -0.2 (p<0.05) Mth 12: -0.6 (p<0.05)
							Hemoglobin A1c (%) [BL to Wk 12, Mth 6, Mth 12]	**Reduced HbA1C** Wk 12: -0.0 (NS) Mth 6: -0.4 (p<0.001) Mth 12: -0.3 (p<0.001)
							Total cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced cholesterol** Wk 12: -7.6 (NS) Mth 6: -26.2 (p<0.001) Mth 12: -30.3 (p<0.001)
							High-density lipoprotein (HDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced HDL cholesterol** Wk 12: -1.0 (NS) Mth 6: -11.4 (p<0.001) Mth 12: +6.2 (p<0.01)
							Low-density lipoprotein (LDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced LDL cholesterol** Wk 12: -5.4 (NS) Mth 6: -6.0 (NS) Mth 12: -27.3 (p<0.001)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Very-low-density lipoprotein (VLDL) – cholesterol (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced VLDL cholesterol** Wk 12: +0.1 (NS) Mth 6: -8.8 (p<0.001) Mth 12: -8.5 (p<0.01)
							Triglycerides (mg/dL) [BL to Wk 12, Mth 6, Mth 12]	**Reduced triglycerides** Wk 12: +2.0 (NS) Mth 6: -38.7 (p<0.001) Mth 12: -37.6 (p<0.01)
							Fasting plasma insulin (uIU/mL) [BL to Wk 12, Mth 6, Mth 12]	**Increased plasma insulin** Wk 12: +0.8 (NS) Mth 6: -3.9 (p<0.001) Mth 12: +4.9 (p<0.001)
							Fasting plasma glucose (mg/dl) [BL to Wk 12, Mth 6, Mth 12]	**Reduced blood glucose** Wk 12: -6 (p<0.01) Mth 6: -11.5 (p<0.001) Mth 12: -13.9 (p<0.001)
							Healthy dietary behavior (food frequency questionnaire) [BL to Wk 12, Mth 6, Mth 12]	**Increased healthy dietary behavior** Processed and refined grains: reduced (p<0.001) More healthy oils: increased (p<0.05) Less healthy oils: reduced (p=0.02) Vegetables: NS Fruits: NS Grains: Wk 12: -0.7 (p<0.01) Mth 6: -0.8 (p<0.01) Mth 12: -0.4 (NS) Meat: Wk 12: -0.2 (NS) Mth 6: -0.5 (p<0.01) Mth 12: -0.1 (NS) Dairy: Wk 12: -0.4 (p<0.05) Mth 6: -0.5 (p<0.01) Mth 12: -0.3 (p<0.01)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Fat: Wk 12: -0.3 ($p<0.01$) Mth 6: -0.4 ($p<0.01$) Mth 12: -0.4 ($p<0.01$)
Venugopal, et al. (2017) [India, SEARO] [13]	Uncontrolled clinical trial	Type II Diabetes Mellitus (Adults)	Yoga-based Lifestyle intervention (Stop Diabetes Movement)	10 days	Nil	1292 (primary outcome data on 896)	Fasting plasma glucose (mg/dL) [BL to Dy 10]	**Reduced blood glucose** -11.2 ($p<0.001$)
Vijayakumar, et al. (2018) [India, SEARO] [14]	Uncontrolled clinical trial	Type II Diabetes Mellitus (Adults) compared with Healthy adults	Group yoga + yoga and diabetes education	60 min/wk group yoga and diabetes education (30 min/wk) for 10 weeks	Healthy adults	310 (189 diabetic, 121 healthy adults)	Fasting plasma glucose (mg/dL) [BL to Wk 10]	**Reduced blood glucose** Group 1 (healthy): NS Group 2 (diabetes): -6.9 ($p=0.01$)
Vinutha, et al. (2015) [India, SEARO] [15]	Uncontrolled clinical trial	Type II Diabetes Mellitus (Adults)	Integrated approach to yoga therapy (IAYT)	1 week	Nil	15	Fasting plasma glucose (mg/dL) [BL to Wk 1]	**Reduced blood glucose** -24.4 ($p<0.05$)
							Heart rate variability [BL to Wk 1]	NS
							Heart rate response to deep breathing [BL to Wk 1]	NS
							Blood pressure response to sustained handgrip (mmHg) [BL to Wk 1]	**Increased BP** +3.2 ($p<0.01$)

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21 Gastrointestinal Conditions

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HIGHLIGHTS

- Gastrointestinal conditions are the second most common reason patients seek naturopathic care.
- The most common gastrointestinal conditions treated by naturopaths/NDs include inflammatory bowel disease, gastroesophageal reflux disease, irritable bowel syndrome, dyspepsia, and/or diarrhea or constipation.
- Within naturopathy, the gastrointestinal system is viewed as central to the health of the whole person with naturopaths/NDs playing a vital role in the recognition of the importance of the microbiome in overall health.
- Naturopaths/NDs use a range of therapies in the treatment of gastrointestinal conditions.
- 82.4% of naturopathic interventions indicated a positive outcome in the treatment of gastrointestinal conditions.
- Additional research investigating the effectiveness of naturopathic care in treating gastrointestinal conditions is warranted.

Gastrointestinal and liver diseases are responsible for approximately 8 million deaths per year worldwide [1]. Furthermore, approximately 48% of Australians and 38% of Americans with gastrointestinal conditions visit at least one complementary medicine practitioner within a 12-month period [2]. Gastrointestinal symptoms and conditions such as inflammatory bowel disease (IBD), gastroesophageal reflux disease (GERD) and/or functional gastrointestinal disorders (such as irritable bowel syndrome (IBS), or functional dyspepsia and/or diarrhea and constipation) are amongst the most common gastrointestinal conditions and reasons people seek care from health care practitioners [3].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=17) naturopathic researchers conducted examining gastrointestinal conditions. This research includes a total of 447 participants and was conducted in the United States of America (USA) (n=5), Australia (n=5), Canada (n=3), Germany (n=2), and India (n=2). The study designs include randomized control trials (n=7), uncontrolled clinical trials (n=4) and case reports/series (n=5). The studied interventions evaluated either single or combination therapies that involved dietary and lifestyle changes (n=7), clinical nutrition (n=6), herbal medicine (n=5), yoga (n=3), and hydrotherapy (n=2).

The main conditions examined in these studies were irritable bowel syndrome (IBS) and functional gastrointestinal disorders (n=7), conditions of the hepatobiliary and pancreatic system (n=5), inflammatory bowel disease (n=2), coeliac disease (n=1), gastrointestinal infection (n=1) and dyspepsia (n=1). Of all the naturopathic clinical studies examining gastrointestinal condition populations, 82.4% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 21.1: Clinical research investigating gastrointestinal conditions conducted by naturopathic researchers.* This body of naturopathic research on gastrointestinal conditions is also supported by 13 observational studies and 39 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Research indicates that the types of gastrointestinal conditions for which people seek naturopathic care may benefit from a range of naturopathic interventions. To date, the number of naturopathic research papers reporting the effects of naturopathic treatments on gastrointestinal health is limited yet employ a diverse range of research methodologies and study designs. Case studies play an important role in presenting the effectiveness of unique individualized treatment approaches which are common in naturopathic care. All studies involving the evaluation of single (herbs, probiotics, yoga) and combined multiple interventions (including diet, yoga, massage, lifestyle, and herbal treatments) indicated positive outcomes in the

primary or secondary measurements. It is also interesting to note that some herbal intervention studies employed multi-botanical formulas and, in some instances, combined herbal treatments with yoga and other therapies. While naturopathic researchers have conducted systematic reviews of herbal medicines for gastrointestinal conditions [4-6], the current clinical research did not employ multiple herbal medicines for gastrointestinal conditions and as such these systematic reviews reflect an important contribution to the literature. The important role of probiotics in the management of gastrointestinal conditions (e.g. antibiotic-associated [7-11] and *Clostridium difficile*-associated diarrhea [12-14]) have also been reviewed by naturopathic researchers.

Within naturopathy, the gastrointestinal system is viewed as central to the health of the whole body [3]. In an international survey of naturopathic practice, gastrointestinal complaints were the second most common reason people sought naturopathic care [3]. The most common gastrointestinal health conditions reported by those using naturopathic services and products are irritable bowel syndrome, gastroesophageal reflux disease, gluten intolerance, coeliac disease, and inflammatory bowel disease [15, 16]. Even for those patients presenting with other health conditions, gastrointestinal health is an important focus of the clinical naturopathic practice [3], and is core to the integrative physiological approach that naturopaths/naturopathic doctors adopt [17].

Although contemporary research is increasingly identifying the important role between gut health and other diseases, addressing this link has always been a core tenet of naturopathic practice [18]. As such, naturopathic researchers have also reviewed published literature examining the intestinal microbiome to provide a clearer understanding of the role it plays in other health conditions [19-23] as well as how it is affected by external factors [19, 24-26]. Overall, there are a substantial number of people with gastrointestinal conditions consulting naturopaths/naturopathic doctors and a longstanding tradition of increased naturopathic focus of gastrointestinal health when compared to other medical systems. When combined with the results of the clinical studies highlighted in this chapter and the additional systematic reviews through which naturopathic researchers have synthesized other existing research, the potential value of naturopaths/ naturopathic doctors and their treatments in the management of gastrointestinal conditions and the need for further research is clearly justified.

Studies based on specific conditions:

Irritable Bowel Syndrome and Functional Gastrointestinal Disorders

Seven naturopathic studies recruited 224 participants with functional bowel disorders. Three [27-29] investigated the effect of orally administered herbal extracts on bowel symptoms, one of which also measured expired breath gases following an oral lactulose challenge [29]. Two studies involved dietary modifications, each based on data obtained by testing serum antibodies to various foods [30, 31]. One study compared a dietary intervention with a yoga intervention [32], and one evaluated the efficacy of digestive enzymes and probiotics on IBS symptoms [33].

Clinical finding

Elimination of foods with positive leucocyte activation test results may reduce symptom severity and improve overall health in individuals with irritable bowel syndrome.

A randomized control trial conducted in USA investigated the effect food elimination and a challenge protocol based on the results of a leucocyte activation test (Alcat) [30]. Adults with IBS (n=55) were randomized to a 4-week elimination diet in which they either avoided foods with positive Alcat assay results and consumed foods with negative assay results (intervention), or eliminated foods with negative assay results and consumed foods with positive assay results (control). Improvements in the intervention arm were observed in measures of IBS Global Improvement Scale (GIS) and continued improvement 4 weeks after completing the intervention (mean group difference 1.22, p=0.02). A greater reduction in IBS-Symptom Severity Scale (IBS-SSS) (mean score reduction 66.42 (p=0.03) was maintained at the conclusion of the intervention.

In a randomized controlled trial conducted in Germany involving a 12-week naturopathic intervention, 59 adults with IBS were randomized to either yoga (75 minutes twice a week) or a diet low in fructo-, oligo-, mono-saccharides and polyols (FODMAPs) [32]. Significant reductions in IBS-SSS were observed for participants in both groups (p<0.001), with abdominal distension scores being significantly lower in the FODMAP group at week 12 (+14.13; p=0.04). No significant between

group difference was demonstrated at week 24. Both interventions had similar efficacy for alleviating overall symptoms associated with IBS. However, those on the yoga had higher QoL scores related to food avoidance (IBS Quality of Life – Food avoidance: +17.1, p=0.005) and less anxiety (Hospital Anxiety and Depression Scale – Anxiety: -1.35; p=0.025) at the conclusion of the study.

Clinical finding

Both yoga and a diet low in fructo-, oligo-, mono-saccharides and polyols (FODMAPs) may reduce symptom severity such as abdominal distension in individuals with irritable bowel syndrome. Yoga may also increase quality of life and reduce anxiety in this population.

Inflammatory Bowel Disease (IBD) and Coeliac Disease

Three studies investigated naturopathic therapies for inflammatory bowel disease or coeliac disease [34-36]. Two studies reported the evaluation of naturopathic approaches/interventions in people suffering inflammatory bowel diseases [34, 36]. A randomized trial conducted in Germany evaluated the effects of yoga in a naturopathic setting in 77 participants with ulcerative colitis following randomization to either 12 weeks of yoga therapy or directed self-care [34]. The participants' disease-specific quality of life, as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ) was significantly improved at the end of the 12-week intervention in the yoga group (+14.7, p=0.02), with benefits sustained at 24 weeks (+16.4; p=0.02). In addition, the Rachmilewitz clinical activity index scores for anxiety were also significantly lower in the yoga group (-1.2; p=0.03).

A randomized controlled trial conducted in Australia with 45 adults with coeliac disease who had persistent symptoms in spite of compliance with a gluten-free diet were recruited [35]. Participants were allocated to receive either a probiotic (n=23) or placebo (n=22) twice daily for 12 weeks. No changes in fecal microbiota were observed except normalization of a baseline difference in *Saccharomyces sp.* counts between the groups (p=0.02 at baseline, p=0.242 at 12 weeks). Urinary d-lactate, a potential indicator of gastrointestinal bacteria metabolomic activity, decreased significantly in the intervention group (p=0.004).

Hepatobiliary and pancreatic system

Of the five papers reporting effectiveness of naturopathic treatments in hepatobiliary and pancreatic conditions, three were case reports [37-39], one a retrospective observational study [40] and one a randomized trial [41].

Clinical finding

St Mary's Thistle *(Silybum marianum)* may reduce ferritin levels in individuals with chronic hepatitis C, particularly those with advanced fibrosis.

In a controlled trial conducted in the USA, 37 patients with chronic hepatitis C (HCV), were randomized to one of three doses of a standardized herbal extract (120 mg silybin from *Silybum marianum*), combined with phosphatidylcholine (IdB 1016) [41]. An HCV genotype 1 was identified in 77.5% of participants with a further 22.5% having either genotype 2 or 3 and 40.5% had at least one of the common hemochromatosis mutations. Clinically elevated serum ferritin levels were identified in 59% of participants at recruitment. At the end of the intervention, serum ferritin levels were reduced in 29 participants (78%) (mean, 244 vs. 215 mug/L; median, 178 vs. 148 mug/L; p=0.0005), with greater reductions observed in those with elevated baseline ferritin, compared to those which were within normal range. Those with more advanced fibrosis (Batts-Ludwig stage III or IV) had the largest reductions in serum ferritin (p=0.015).

Other Gastrointestinal Conditions

Two other studies investigated prevention of gastrointestinal infections [42] and dyspepsia [43], respectively. A randomized controlled trial conducted in Australia over 17 weeks (following a 10-week control period) evaluated the effects of a naturopathic probiotic protocol on the incidence of gastrointestinal infections in elite rugby players [42]. The 19 athletes were randomized to receive either a probiotic or placebo twice daily for 17 weeks. Participants in the probiotic group had a reduced incidence of gastrointestinal infection over the course of the study, and higher salivary a-amylase (+16.2 vs +8.1, p=0.007), a potential marker for host defense.

A randomized controlled trial conducted in Canada evaluated the effect of 30 days of administration of inositol hexaniacinate (IHN), 1782 mg /day for 30 days, on fasting gastric pH and symptoms associated with dyspepsia in 22 participants [43]. Results at completion were evenly divided between those in the active and placebo

arms. Symptoms, as measured by the Gastrointestinal Symptom Questionnaire (GSQ), were reduced from 10.73 to 8.45 in those receiving IHN. Gastric pH reduced significantly in both groups (both $p<0.01$) and study participants receiving placebo reported similar rates of adverse effects as those receiving IHN. The authors report that compliance was suboptimal in both groups. Analysis of baseline data revealed no correlation between fasting gastric pH and GSQ scores.

Table 21.1 Clinical research investigating gastrointestinal conditions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
Ali, et al. (2017) [USA, AMRO] [30]	Randomized controlled trial	Irritable bowel syndrome	Dietary elimination based on leucocyte antigen test results (LATR)	4 weeks elimination, systematic *ad lib* re-introduction over 4 weeks	Elimination contrary to LATR	55 (26/29)	IBS Global Improvement Scale [BL to Wk 4, Wk 8]	**Reduced** Wk 4: -0.86 (p=0.04) Wk 8: -1.22 (p=0.04)
							IBS Severity Scoring System [BL to Wk 4, Wk 8]	**Reduced** Wk 4: -61.78 (p=0.04) Wk 8: -66.42 (p=0.05)
							IBS Adequate Relief Scale [BL to Wk 4, Wk 8]	NS
							IBS-Quality of Life [BL to Wk 4, Wk 8]	NS
Bares, et al. (2008) [USA, AMRO] [41]	Uncontrolled clinical trial	Hepatitis C (chronic)	Standardized silybin and soy phosphatidylcholine complex (IdB 1016) 314mg with 120mg silybin per capsule	12 weeks Dose 1: 314mg TD Dose 2: 628mg TD Dose 3: 942mg TD	Nil	37	Serum iron (ug/dL) [BL to Wk 12]	NS
							Total Iron binding capacity (ug/dL) [BL to Wk 12]	NS
							Transferrin iron saturation (%) [BL to Wk 12]	NS
							Serum ferritin, by dose (ug/L) [BL to Wk 12]	**Reduced ferritin** All participants: -30 (p=0.0005) Dose 1: -51 (p=0.004) Dose 2: -13 (p=0.03) Dose 3: NS
							Serum ferritin, by stage of fibrosis (ug/L) [BL to Wk 12]	**Reduced ferritin (Stage III and IV)** Stage II: NS Stage III: -36 (p=0.005) Stage IV: -16 (p=0.01)
							Liver enzymes [BL to Week 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
Carter, et al. (2019) [Australia, WPRO] [27]	Case series	Functional gastrointestinal disorder	Case 1: *Botanical medicines* – Flordis Iberogast liquid herbal formula containing, *Foeniculum vulgare* seed, *Gentiana lutea* root, chamomile, or dandelion root teas; *Nutritional supplements* – Bioceuticals MultiGest Enzymes, Metagenics CalmX; *Lifestyle advice* – mindfulness/meditation practices, mindful eating, exercise, self-massage. *Dietary advice:* plant based whole foods, fiber, low FODMAP, bone broths. Case 2: *Botanical medicines* – Liquid herbal formula containing *Matricaria chamomilla* 1:2, *Cynara scolymus* 1:2, *Taraxacum officinale* radix 1:2, *Althea officinalis* 1:5, *Lavandula angustifolia* 1:2; *Eschscholzia californica* 1:2; *Scutellaria lateriflora* 1:2; *Lifestyle advice* – sleep hygiene, mindful eating; *Dietary advice* – apple cider vinegar, protein, legumes, vegetables, fruit, fibrous food. 5 weeks treatment.	Case 1: 3 Visits Case 2: 4 Visits	Nil	2	Gastrointestinal Symptom Rating Scale (self-reported) [BL to Visit 2, 3, 4]	**Reduced symptoms** Case 1: Visit 2, -5 Visit 3, -2 Total, -2 Case 2: Visit 2, -6 Visit 3, -6 Visit 4, -11 Total, -11
Cramer, et al. (2017) [Germany, EURO] [34]	Randomized controlled trial	Ulcerative colitis	Yoga: 90 min (Hatha yoga class) plus optional daily practice	Weekly for 12 weeks	Written self-care advice (evidence-based informative books)	77 (39/38)	Inflammatory Bowel Disease Questionnaire [BL to Wk 12, 24]	**Increased quality of life** Wk 12 Yoga: +16.3 Self-care: +0.8 Between group: +14.7 (p=0.02) Wk 24 Yoga: +21.5 Self-care: +9.6 Between group: +16.4 (p=0.02)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
							Rachmilewitz clinical activity index [BL to Wk 12, 24]	**Reduced disease activity** Wk 12 – NS Wk 24 Yoga: -1.8 Self-care: +0.8 Between group: -1.2 (p=0.03)
Fathima-Jebin, et al. (2018) [India, SEARO] [37]	Case report	Non-alcohol fatty liver disease and ascites	Integrated naturopathy & yoga therapy (IYNT) (yoga, acupuncture, massage, hydrotherapy, chromotherapy, mud therapy, reflexology) Diet therapy	20-30 min/ session Varied: 4-12 sessions each in 30 days	Nil	1	Weight (kg) [BL to Dy 30]	**Reduced weight** - 4
							Body mass index (BMI) (kg/m2) [BL to Dy 30]	**Reduced BMI** -1.5
							Abdominal girth (cm) [BL to Dy 30]	**Reduced abdominal girth** -5
							Blood pressure (BP) [BL to Dy 30]	**Reduced BP** Systolic: -10 Diastolic: -2
							CT imaging of liver density [BL to Dy 30]	**Reduced liver density** BL: 12.4cm x 12cm x 9.3cm Dy 30: 12.8cm x 9cm x 8.6cm
							CT fluid estimate [BL to Dy 30]	**No change**
							Fasting plasma glucose (mg/DL) [BL to Dy 30]	**Reduced fasting glucose** -7
							Postprandial glucose (mg/dL) [BL to Dy 30]	**Reduced post-prandial glucose** -2
							Bilirubin, total (mg/dL) [BL to Dy 30]	**Reduced total bilirubin** -0.03
							Bilirubin, direct (mg/DL) [BL to Dy 30]	**Reduced direct bilirubin** -0.11
							Alkaline phosphatase (ALP) (U/L) [BL to Dy 30]	**Reduced ALP** -11

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
							Aspartate transaminase (AST) (U/L) [BL to Dy 30]	**Reduced AST** -4.1
							Alanine transaminase (ALT) (U/L) [BL to Dy 30]	**Reduced ALT** -8.3
							Gamma-glutamyl transaminase (GGT) (U/L) [BL to Dy 30]	**Reduced GGT** -6
							Urea (mg/dL) [BL to Dy 30]	**Reduced urea** -31.3
							Creatinine (mg/dL) [BL to Dy 30]	**Reduced creatinine** -0.26
							Uric acid (mg/dL) [BL to Dy 30]	**Reduced uric acid** -4.9
Harnett, et al. (2016) [Australia, WPRO] [35]	Randomized controlled trial	Coeliac disease	Probiotics (VSL #3) 450 bill CFU per sachet, with meals	1 sachet 2x/day X 12 weeks	Placebo	42 (21/21)	Fecal microbial counts [BL to Wk12]	NS
							Urinary organic acids [BL to Wk12]	**Reduced** Reduction in urinary D-lactate (p=0.004)
Hawrelak & Myers (2010) [Australia, WPRO] [28]	Uncontrolled clinical trial	Irritable bowel syndrome	DA-IBS: *Vaccinnium myrtillus* (dried, powdered) 10g, *Ulmus fulva* 4.5g, *Agrimonia eupatoria* (aerial parts) 3g, and *Cinnamonium zelanicum* 1.5g C-IBS: lactulose 3g, *Ulmus fulva* 7g, *Glycyrrhiza glabra* 1.5g, *Avena sativa* (bran) 2g.	Twice daily in 250mL apple juice for 3 weeks	Nil	31 (21/10)	Bowel movements per day [BL to Wk 3]	**Reduced bowel movements (Diarrhea subtype)** DA-IBS: -0.19 (p=0.03) **Increased bowel movements (Constipation subtype)** C-IBS: +0.22 (p=0.02)
							Consistency of stool [BL to Wk 3]	**Increased stool consistency (Constipation subtype)** DA-IBS: NS C-IBS: +0.67 (<0.0001)
							Sense of straining [BL to Wk 3]	**Reduced sense of straining** DA-IBS: -0.19 (0.004) C-IBS: -0.74 (<0.0001)
							Sense of urgency [BL to Wk 3]	DA-IBS: NS C-IBS: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
							Abdominal pain [BL to Wk 3]	**Reduced abdominal pain** DA-IBS: -0.19 (p=0.006) C-IBS: -0.20 (p=0.03)
							Bloating severity [BL to Wk 3]	**Reduced bloating severity** DA-IBS: -0.32 (p<0.0001) C-IBS: -0.19 (p=0.03)
							Flatulence severity [BL to Wk 3]	**Reduced flatulence (Diarrhea subtype)** DA-IBS: -0.25 (p=0.0001) C-IBS: NS
							Global symptom severity [BL to Wk 3]	**Reduced overall symptoms** DA-IBS: -0.40 (p=0.002) C-IBS: -0.71 (p=0.0005)
Kennedy, et al. (2014) [Canada, AMRO] [31]	Uncontrolled clinical trial	Irritable bowel syndrome	Elimination/reintroduction diet based on the results of non-IgE mediated food allergy test	4 wk elimination 8-food challenges over 4 weeks	Nil	4	Non-IgE food allergy tests [BL to Wk 4]	NS
							Symptoms [BL to Wk 4]	NS
							IBS Symptom Severity Scale [BL to Wk 4]	NS
Kim, et al. (2006) [USA, AMRO] [33]	Randomized controlled trial	Functional gastrointestinal disease	Probiotics & nutrients Group 1: 50mill CFU x6 *spp* AND grass juice, fulvic acid derived minerals Group 2: 50mill CFUx12 *spp* AND grass juice, fulvic acid derived minerals Group 3: C. 50mill CUF x5 *spp* AND Mixed mushroom/algae Group 4: 50mill CFU x6 *spp* Group 5: Grass juice, fulvic acid derived minerals	12 weeks: 4-week run-in 8 weeks of 4 cap TD	Placebo	72 (12/12/12/12/12)	Gastrointestinal Quality of Life Index [BL to Wk 12]	NS
							Gastrointestinal Visual Analogue Scales (bloating, gas, abdominal discomfort, indigestion, constipation, diarrhea) [BL to Wk 12]	NS
							Urinary lactulose-mannitol challenge test [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
Logan and Beaulne (2002) [Canada, AMRO] [29]	Case report	Irritable bowel syndrome	Enteric Coated Peppermint oil (Herbal/ aromatherapy)	0.2mL TD 20 days	Nil	1	Lactulose Hydrogen Breath Test [BL to Day 20+6]	**Reduced breath test** Hydrogen: Fasting -6ppm 20 min -19ppm 60 min -22ppm Methane: Fasting -0.0ppm 20 min -2.0ppm 60 min -0.0pm
							Self-reported symptoms [BL to Day 20]	**Decreased bloating, pain, eructation, improved frequency of bowel function**
Milliman. et al. (2000) [USA, AMRO] [40]	Retrospective observational study	Hepatitis C	All patients: (a) Silymarin 80% standardized extract (150 mg); (b) d-alpha tocopherol (400IU), vitamin C (500 mg), beta carotene (15 mg), selenium amino acid chelate (50 mcg) (c) N-acetyl-L-cysteine (1000mg); (d) cod liver oil 1-2 tsp daily (e) dietary and lifestyle advice including breakfast muesli. (f) colchicine (1.2 mg); (g) ursodeoxycholic acid (300 mg) Some patients: (h) herbal mixture of *Phyllanthus nigrum or amarus*, *Picrorrhiza kurroa*, *Zingiber officinale*, *Boerhaavia diffusa*, *Andrographis paniculata*, *Cichorium intybus*, *Emblica officinalis*, *Embelia ribes*, *Terminalia chebula*, *Terminalia arjuna*, *Piper longum*, and *Eclipta alba* (i) deglycyrrhizinated licorice 500mg	Minimum one month treatment. All patients: (a), (b) and (c) twice daily; (d) once daily; (e) daily; (f) daily, five days per week; (g) twice daily Some patients: (h) twice daily; (i) two to four time daily	Nil	14	Alanine aminotransferase (ALT) (U/L; % reduction)	**Reduced ALT** -35 U/L (p=0.026) Reduction of greater than 25%: 7 of 14 patients
							Self-reported symptoms of advancing liver disease (liver pain, enlarged liver, jaundice, ascites, generalized edema, or liver-related bowel dysfunction)	None
							Self-reported symptoms of wellbeing	Most patients reported an increased sense of well-being on the treatment program.

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
Prousky and Seely (2011) [Canada, AMRO] [43]	Randomized controlled trial	Non-ulcer dyspepsia	Inositol hexaniacinate (IHN) (540mg crystalline niacin and 54mg inositol)	3 capsules OD, 4 weeks	Placebo	22 (11/11)	Gastrointestinal Symptom Questionnaire	NS
							Gastro-test® pH	NS
Pumpa, et al. (2019) [Australia, WPRO] [42]	Randomized controlled trial	Prevention of gastrointestinal infection (elite rugby players)	Probiotics (Ultrabiotic 60 and SB Floractiv)	Total duration: 27 weeks (Control period, Wk1-10; Ultrabiotic 60 introduced, Wk11-17; SB Floractiv introduced, Wk18-27)	Placebo	19 (11/8)	Incidence of GI infection [BL to Wk 17]	**Reduced incidence**
							Salivary Immunoglobulin A (U/mL) [BL to Wk 17]	NS
							Salivary alpha-amylase (U/mL) [BL to Wk 27]	**Increased salivary alpha-amylase** Wk 10: NS Wk 17: NS Wk 27: Probiotics +16.2 Placebo +8.1 Between group p=0.007
							Salivary cortisol (ug/dL) [BL to Wk 27]	**Increased cortisol** Wk 10: NS Wk 17: Probiotics +0.02 Placebo -0.01 Between group p=0.02 Wk 27: Probiotics -0.01 Placebo -0.05 Between group p=0.001
Revadi, et al. (2018) [India, SEARO] [38]	Case report	Hepatic cirrhosis & ascites	Integrated naturopathy & yoga therapy (yoga, acupuncture, massage, hydrotherapy, mud therapy) Diet therapy (vegetarian) + Ayurvedic treatment & furosemide (from pre-baseline)	Various, over 4 weeks	Nil	1	Blood pressure (mmHg) [BL to Wk 4]	**Reduced BP** Systolic: -10 Diastolic: -12
							Weight (kg) [BL to Wk 4]	**Reduced weight** -17
							Body mass index (kg/m2) [BL to Wk 4]	**Reduced BMI** -6.3
							Abdominal girth (in)	**Reduced abdominal girth** -12
							Breath holding time (seconds)	**Increased breath holding** +6

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
							Bilirubin, total (mg/dL) [BL to Wk 4]	**Reduced total bilirubin** -0.6
							Bilirubin, direct (mg/DL) [BL to Wk 4]	**Reduced direct bilirubin** -0.2
							Serum albumin (g/dL) [BL to Wk 4]	**Increased albumin** +1.3
							Aspartate aminotransferase (AST) (U/L) [BL to Wk 4]	**Reduced AST** -6
							Alanine transaminase (U/L) [BL to Wk 4]	**Reduced ALT** -14
							Urea (mg/dL) [BL to Wk 4]	**Reduced urea** -8
							Creatinine (mg/dL) [BL to Wk 4]	**Reduced creatinine** -0.4
Schumann, et al. (2018) [Germany, EURO] [32]	Randomized controlled trial	Irritable bowel syndrome	Low FODMAP diet (nutritional counselling including an educational group lecture, 2 individual counselling and 1 group counselling sessions; low-FODMAP recipes, lists of foods to avoid)	12 weeks (+12 week follow up): Low FODMAP diet – nutritional counselling x 4, individual counselling x 2; group counselling x 1; Yoga – 75 min, 2x/week	Yoga	59 (29/30)	IBS Symptom Severity Scale – Total [BL to Wk 12, 24]	**Decreased abdominal distension** Wk 12: Total NS Duration of pain NS Severity of pain NS Abdominal distension -14.13, p=0.04 Bowel satisfaction NS Interference with life NS Wk 24: NS
							IBS Quality of Life – Dysphoria [BL to Wk 12, 24]	**Increased food avoidance** Wk 12: Dysphoria NS Interference with activity NS Body image NS Health worries NS Food avoidance +17.1 (p=0.005) Social reaction NS Sexual NS Relationships NS Overall NS Wk 24: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
							Perceived Stress Questionnaire [BL to Wk 12]	NS
							Cohen Perceived Stress Scale [BL to Wk 12]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 12]	**Reduced anxiety** Anxiety: Wk 12 -1.35 (p=0.03) Wk 24 NS Depression: Wk 12 NS Wk 24 NS
							Short Form-36 [BL to Wk 12]	NS
							Body Responsiveness Scale [BL to Wk 12]	NS
							Body awareness questionnaire [BL to Wk 12]	**Increased body awareness** Wk 12: NS Wk 24: +7.6 (p=0.02)
Sinclair (2015) [Australia, WPRO] [39]	Case report	Acute pancreatitis	Dietary changes: avoid coffee, stimulants, purified sugar and fatty meals; increase nutrient- and phytochemical-dense foods; Vegetable soup (butter, onions, garlic, carrot, celery, cauliflower, broccoli, zucchini) cooked for 2-3 hours in a base of *Curcuma longa* (3 tablespoons, dried), *Zingiber officinale* (1 tablespoon, fresh), *Allium sativum* (3 bulbs, fresh), *Coriandum sativum* (1 bunch, leaf and roots; 2 tablespoons, dried), *Cuminum cyminum* (1 tablespoon, dried) *Illicium verum* (3 x fruit), *Foeniculum vulgare* (1 tablespoon, crushed seed),	Day 1: Dietary changes and herbal medicines Day 2: Herbal medicines and exercise	Nil	1	Pain	**Reduced pain** Resolved within 1 hour
							Nausea	**Reduced nausea** Resolved within 1 hour
							Bowel motions	**Reduced bowel motions** Normalised on day 2 of treatment

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/Control)	Measure of Outcome	Outcome
			Ellettaria cardamomum (5 x pods), *Piper nigrum* (1/2 teaspoon) Herbal medicines: *Ulmus rubra* (2 tablespoons); *Plantago ovata* (2 tablespoons); *Zingiber officinale* and *Matricaria chamomilla floz* infusion Exercise: Gentle hike in local nature reserve (6km; 3 hours)					
Suskind, et al. (2013) [USA, AMRO] [36]	Uncontrolled clinical trial	Inflammatory Bowel Disease (pediatric)	Curcumin in addition to standard therapy.	500mg BD x 3 weeks 1g BD x 3 weeks 2g BD x 3 weeks	Nil	9	Pediatric Ulcerative Colitis Index (<30) [BL to Wk 3]	**Remission** -20 pts in 2 patients (=remission)
							Pediatric Crohn's Disease Activity Index (<34) [BL to Wk 3]	**Reduced symptoms** -5 (to 0) in 1 patient

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22 Mental Health Conditions

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HIGHLIGHTS

- Mental health concerns – including anxiety, depression, obsessive compulsive disorder, stress, and various forms of psychosis – are the third most common reason for patients seeking naturopathic care.
- The naturopathic approach recognizes the connection between a patient's psychological state and their functional and structural conditions.
- The naturopathic community has been active in codifying herbal medicine, lifestyle and nutritional approaches to mental health treatment into contemporary practice.
- 64.7% of clinical studies investigating naturopathic treatment for mental health conditions report a positive outcome in at least one primary or secondary outcome measure.

Mental health is an integral and essential component of overall health. According to the World Health Organization (WHO) constitution, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [1]. Mental health encompasses emotional well-being (happiness, interest in life), psychological well-being (good relationships, managing responsibilities of daily life, satisfied with life) and social well-being (being able to contribute and be part of society) [2]. Mental health disorders involve changes in emotion, thinking and/or behaviour including conditions such as depression, anxiety, bipolar disorders, schizophrenia and other psychoses or mental health conditions. It is affected by socioeconomic, lifestyle and environmental factors and is a comorbidity of many other symptoms and conditions. The rate of mental health disorders is increasing around the world with the WHO 2019 statistics indicating that 20% of children and adolescents suffer from a mental health disorder [3]. As of 2016, mental and addictive disorders affected more than 1 billion people globally, caused 7% of the total burden of disease and 19% of all years lived with disability [4].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=31; published in 34 papers) naturopathic researchers conducted to investigate treatments for mental health conditions. This research includes 2,264 participants and was conducted in Australia (n=18), the United States of America (USA) (n=6), India (n=5) and Canada (n=5). The study designs include randomized control trials (n=22), case reports (n=3), uncontrolled trials (n=3), retrospective cohort study (n=1), non-randomized controlled studies (n=2) and secondary analysis (n=3). The studied interventions featured a range of therapeutics, prescribed both as a single intervention and with more than one intervention including clinical nutrition (n=14), yoga (n=6), herbal medicine (n=12), complex naturopathic intervention (n=4), dietary and lifestyle change (n=4), acupuncture (n=2), homeopathy (n=1) and mind-body medicine (n=1).

The conditions examined in these studies included depression (n=14), anxiety (n=13), stress (n=2), schizophrenia (n=1), obsessive compulsive disorder (n=2), sleep disorder (n=2), smoking cessation (n=1), bipolar disorder (n=1), eating disorder (n=1) and psychotic episode (n=1). Of all the naturopathic clinical studies examining mental health populations, 64.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 22.1: Clinical research investigating mental health conditions conducted by naturopathic researchers.* This body of naturopathic research on mental health is also supported by over 50 observational studies and more than 80 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Mental health conditions including anxiety, depression, obsessive compulsive disorder (OCD), stress and various forms of psychosis are the third most common reason for patients to seek naturopathic care [5]. Naturopathic research indicates that mental health conditions may benefit from naturopathic care. The research in mental health has focused on several naturopathic interventions with herbal medicines, nutraceuticals and yoga having the most notable clinical effects.

Naturopaths/naturopathic doctors recognize that mental and psychological health is affected by functional and structural disorders [6]. The broad-spectrum approach to health and disease and the naturopathic principle *Treat the Whole Person* is well-suited when working with patients with mental health disorders as it acknowledges the significance of a person's mental status when treating any condition. For this reason not only have naturopaths/naturopathic doctors been able to lead the development of theoretical and research development of fields such as nutritional psychiatry [7, 8], but have also played a leading role in understanding how this knowledge can be effectively translated into practice, particularly with respect to effectively individualizing treatment [9].

The naturopathic community has been active in translating traditional approaches to mental health treatment into contemporary practice, leading the development of research and practice guidelines on herbal medicine, lifestyle and nutritional support [7, 10-12]. Addressing mental and emotional health concerns also has the potential to improve outcomes for other clinical disorders as part of a holistic care model, and naturopathic approaches to health align well with this paradigm. Given the significant prevalence of patients with mental health concerns seeking naturopathic care, it is important that high-quality research in this area be continued, and that integrative models incorporating naturopathic care in mental health are evaluated.

Studies investigating specific conditions:

Depression

Fourteen studies, involving 1,160 participants, conducted in Australia (n=8), India (n=4), Canada (n=1) and the USA (n=1) investigated naturopathic approaches and interventions for depression. Seven of the interventions included the use of individual or combination nutraceuticals (clinical nutrition) [13-19], five included mind-body medicine interventions including four that investigated yoga therapy [20-23], and one that investigated meditation as a component of yoga therapy practice [24] and three investigated herbal medicine [25-27].

Clinical finding

A combination of Kava *(Piper methysticum)* and St John's wort *(Hypericum perforatum)* may reduce symptoms of depression in individuals with major depressive disorder with comorbid anxiety.

A randomized, double blind placebo-controlled study (n=28) conducted in Australia explored the efficacy of *Hypericum perforatum* (St. John's wort flowering tops, SJW) and *Piper methysticum* (Kava rhizome) in adults with major depressive disorder (MDD) with comorbid anxiety [26]. This study used two subsequent crossover phases of 4 weeks each following a two-week placebo-run, with individuals receiving 1.8g standardized tablets of SJW and 2.66g standardized tablets of Kava, three times per day each. Participants in the intervention arm had a greater reduction in symptoms of depression (assessed by the Beck Depression Inventory (BDI)) compared to placebo.

A pilot dosage-condition blinded controlled trial (n=26) conducted in Australia investigated the effect of S-adenosylmethionine (SAMe) in combination with magnesium orotate in adults (>18 years of age) with MDD who reported a previous suboptimal response to selective-serotonin reuptake inhibitors (SSRIs) [14]. Participants received either 800mg per day (400mg BID) or 1600mg (800mg BID) of SAMe for 15 weeks. Participants who showed no response to treatment after the first 7 weeks (n=8) received 1600mg per day of magnesium orotate as an adjunct to SAMe for an additional 8 weeks. Both groups of participants reported a reduction in BDI scores (SAMe only: -26.8, $p<0.001$; SAMe & magnesium: -19.3; $p=0.001$), reduced functional distress assessed via the Outcome Questionnaire 45 (OQ45) (SAMe only: -56.9, $p<0.001$; SAMe & magnesium: -32.4; $p<0.001$), and increased quality of life (SAMe only: +23.2; $p<0.001$; SAMe & magnesium: +20.8; $p=0.001$) compared to baseline. No difference was noted between participants receiving 800mg or 1600mg of SAMe daily.

An additional open-label pilot trial (without placebo control) conducted in Australia explored the role of omega-3 fatty acids in adults with mild to moderate MDD who were previously non-responsive to medication or psychotherapy using a low dose of DHA (260 mg or 520 mg/day) without EPA [19]. There was a significant effect on depressive symptoms, as assessed by total change in the Hamilton Depression Rating Scale (HAM-D) scores (-10.33; $p<0.001$) and the proportion of participants with a clinical response to treatment ($\geqslant$ 50% reduction in HAM-D scores) (54%) or achieving remission [(HAM-D score = 0) (46%) ($p<0.0001$)]. Participants also reported

reduced severity in overall symptoms (Clinical Global Impression Severity Scale: -1.28; p<0.05).

A comparative randomized controlled trial conducted in Australia explored the effect of "Mental silence" Meditation (Sahaja yoga) compared to a "Relaxation" active control and a waitlist group [24]. The intervention was delivered via twice weekly 1-hour sessions plus twice daily 10-20 minutes practice at home for 8 weeks. This randomized controlled trial involved 178 adults and found both groups achieved a significant improvement in psychological strain, measured by the Psychological Strain Questionnaire (PSQ), compared with placebo (meditation: -37.0; relaxation: -22.3; waitlist: -17.5). However, only participants in the mediation group reported reduced depressive symptoms as assessed by the Depression-Dejection (DD) subscale of the Profile of Mood States (POMS) (meditation: -3.0; relaxation and no treatment no significant change p=0.019).

Anxiety

Thirteen studies from Australia (n=7), Canada (n=5) and the USA (n=1) addressed naturopathic approaches and interventions for anxiety. Four studies investigated the use of herbal medicines: three using *Piper methysticum* (Kava) in adults with a range of anxiety disorders [28-30], and the fourth a standardized dose of *Bacopa monnieri* in adults >65 years of age with anxiety and depression without signs of dementia [25]. Two studies examined the impact of clinical nutritional supplementation on anxiety – one involving epigallocatechin gallate (EGCG) and conjugated linoleic acid (CLA) [31] and one the impact of L-theanine (an amino acid typically derived from Green Tea) in adults with generalized anxiety disorders (GAD) [32]. One study investigated the use of a homeopathic preparation (*Argentum nitricum* 12X) in university students with test anxiety [33]. Two studies evaluated whole-person naturopathic care: one combining a botanical medicine preparation, multi-vitamin therapy, and lifestyle counselling in adults with anxiety [34], the second exploring whole-person naturopathic care in individuals with anxiety and depression [13]. One case report looked at the impact of dietary modifications on anxiety [35]. Finally, one study investigated the use of acupuncture, cupping, and/or herbal ear seeds in children and adolescence with GAD [36].

Clinical finding

Kava *(Piper methysticum)* may also reduce symptoms of anxiety in adults with generalized anxiety disorder.

Two randomized, double blind placebo-controlled studies conducted in Australia found *Piper methysticum* (Kava) extracts to reduce anxiety in adults with GAD without major depression. Both studies compared standardized extracts (ranging between 120 and 250mg kavalactones per day) to inert identical tablets (placebo control). The first study (n=60) compared a standard dose of 250mg kavalactones/day in adults over the age of 18 who had experienced at least 1 month of generalized anxiety (>10 on the Beck Anxiety Inventory) to a placebo. The study found reduced anxiety (Hamilton Anxiety Scale: p<0.0001; Beck Anxiety Inventory; p=0.001) and depression (Montgomery-Asberg Depression Rating Scale: p=0.003) favoring the Kava group [28]. The second study (Phase I n=58, Phase 2 n=29) explored the effect of two doses (120mg and 240mg of Kava extract) and found statistically significant reduction in Hamilton Anxiety Rating Scale (HAM-A) in adults with GAD without comorbid mood disorder (p=0.05) [30]. Participants received the higher dose of 240mg if they were deemed non-responders by week 3 of this 6-week trial. Effect sizes were more pronounced in those individuals with moderate to severe pre-intervention anxiety (p=0.02). Researchers also identified two polymorphisms in the GABA transporter that were associated with greater HAM-A reduction in the Kava treatment group (rs2601126: p=0.02; rs2697153: p=0.046).

Clinical finding

Whole-person naturopathic care involving herbal medicine, clinical nutrition, dietary counselling, and lifestyle modification – in addition to breathing exercises and psychotherapy/counselling – may reduce fatigue, body mass index and patient-prioritized symptoms in individuals with anxiety.

A randomized control study conducted in Canada compared the efficacy of individualized whole-person naturopathic care with psychotherapy in Canadian Post employees with anxiety (Beck Anxiety Inventory >10) without comorbid depression [34]. Naturopathic care consisted of *Withania somnifera* (300mg BID) herbal extract, a multi-vitamin (BID) and naturopathic dietary and lifestyle counselling. Both groups also received training in diaphragmatic breathing, encouragement to exercise, cognitive behaviour therapy, and stress reduction counselling. Based on the between group analysis, the naturopathic care intervention group reported reduced fatigue across all domains of the Fatigue Questionnaire: subjective (-18.0; p<0.001), physical (-13.19; p=0.0033), motivation (-20.32; p<0.0001) and concentration (-17.51; p<0.0001). Reductions in self-prioritized symptoms, recorded using the Measure Yourself Medical Outcomes (MYMOP) instrument, also favored the *Withania*

somnifera group (Symptom 1: -1.77, p<0.0001; Symptom 2: -1.08, p=0.0115) and reduced weight (-1.47; p=0.00146) and reduced body mass index (-0.56; p=0.00128).

Other mental health conditions

Studies investigated other health conditions such as obsessive-compulsive disorder [37, 38], schizophrenia and psychotic disorders [39-41], eating disorders [42], smoking cessation [43], sleep disorders [44, 45], and chronic psychological stress [46].

Clinical finding

N-acetyl cysteine may reduce compulsive behaviours in individuals with obsessive compulsive disorder.

A randomized control trial and a secondary analysis conducted in Australia examined adults (18 – 70 years old) with DSM-5-diagnosed obsessive-compulsive disorder (OCD) taking 1.5 grams of N-acetyl-cysteine (NAC) orally twice per day for 16 weeks [37, 38]. It observed significant interaction in the 'Compulsions' subscale of the Yale-Brown Obsessive Compulsive Scale (YBOCS) in those taking NAC (p=0.013), with a significant reduction in compulsion observed at week 12 (dissipating at week 16) [37] and a significant decrease in the YBOCS compared to a placebo for participants under 34 years of age (p=0.037) [38].

An uncontrolled trial conducted in the USA explored the effect of whole-person naturopathic care in a population of patients with bipolar disorder presenting to a Community Health Center [41]. Individuals who scored a minimum of 10 on the Patient Health Questionnaire depression screener (PHQ-9) and Generalized Anxiety Disorder 7-item scale (GAD-7) and returned for care on at least two occasions over 26 months were entered into the trial (n=60). Interventions consisted of personalized recommendations for treatment including but not limited to nutraceuticals, pharmaceuticals, homeopathics, and/or herbal medicines. Improvement was measured as a greater than 50% reduction based on initial anxiety or depression scores. There was a significant reduction in both anxiety (50.0% saw improvement in GAD-7 scores) and depression (58.6% saw improvement in PHQ-9 scores). Another uncontrolled trial conducted in India of adult schizophrenia patients stabilized on antipsychotic medication for 6 weeks found significant reduction in symptoms (Scale for Assessment of Negative Symptoms: -30.36, p<0.001; Scale for Assessment of Positive Symptoms: -21.34, p<0.001) and social disability (Groningen social disability scale: -25.01, p<0.001) but increased social cognition (Social Cognition composite score: +18.97, p<0.001) after 6 weeks (20 sessions) of 1-hr yoga sessions [39].

Table 22.1 Clinical research investigating mental health conditions conducted by naturopathic researchers

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Aucoin and Bhardwaj (2016) [Canada, AMRO] [35]	Case report	Generalized anxiety disorder (with hypoglycemia symptoms)	Macronutrient modification – Increased dietary intake of protein, fat, and fiber	4 weeks	Nil	1	Anxiety symptom severity [BL to Wk 4]	**Reduced anxiety** Wk 4 (8/10 to 4 or 5/10)
							Subjective symptoms [BL to Wk 4]	**Reduce symptoms** Increased energy Reduced frequency and intensity of hypoglycemic symptoms Reduced headaches (once per wk compared to everyday). Cessation of chronic vaginal discharge.
Aucoin (2017) [Canada, AMRO] [13]	Case report	Mood and anxiety disorders (depressive disorder and social anxiety disorder)	Breakfast smoothies, increased vegetable intake, herbal formula *(Hypericum perfortum*, *Passiflora incarnata, Valeriana officinalis)* and fish oil supplement (750mg EPA, 500mg DHA) exercise 45min twice weekly, ferrous bisglycinate chelate (36mg) and B12 1000ug/ day sublingual	4 weeks	Nil	1	Subjective mood and anxiety symptoms [BL to Wk 4]	**Reduce symptoms** Improved mood at each return visit, increased tolerance to anxiety provoking situations, increased energy and no headaches
Baker, et al. (2003) [Australia, WPRO] [33]	Randomized controlled trial	Anxiety (university students 18.5-52.2yo scoring > 50 on Benson Revised Test Anxiety Scale)	1st arm: traditionally prepared *Argentum nitricum* 12X 2nd arm: radionically prepared *Argentum nitricum* 12X 3rd arm: placebo	5 drops of preparation in 30 ml of water twice daily for 4 consecutive days	Placebo	62	Revised Test Anxiety Scale [BL to Dy 4]	NS
							Test Anxiety Scale [BL to Dy 4]	NS
							A. nitricum profile questionnaire	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Bambling, et al. (2015) [Australia, WPRO] [14]	Randomized controlled trial	Major Depressive Disorder (adults > 18 years of age with previous suboptimal response to SSRI)	S-adenosylmethionine (SAMe) and 8 mg Magnesium Orotate as adjunct to SSRI	1600 mg (800mg BID) or 800 mg (400mg BID) daily of SAMe for 15 weeks. Non-responders supplemented with 1600 mg (800mg BID) of Magnesium Orotate for 8 weeks	nil	26 (14/12)	Beck Depression Inventory [BL to Wk 15]	**Reduced depression** SAMe: -26.8 (p<0001) NS difference between 800mg and 1600mg dose of SAMe. SAMe & Mg: -19.3 (p=0.001)
							Outcome Questionnaire 45 [BL to Wk 15]	**Reduced functional distress** SAMe: -56.9 (p <0.001) SAMe & Mg: -32.4 (p<0.001)
							Quality of Life [BL to Wk 15]	**Increased quality of life** SAMe: +23.2 (p<0.001) SAMe & Mg: +20.8 (p=0.001)
							ICD-DSM Mini International Neuropsychiatric Interview [BL to Wk15, Wk25]	NS
							Depression, Anxiety and Stress Scale [BL to Wk15, Wk25]	NS
							Structured Interview for the DSM-IV [BL to Wk15, Wk25]	NS
Bier, et al. (2002) [USA, AMRO] [43]	Randomized controlled trial	Smoking cessation	Auricular acupuncture bilaterally at five ear points and one wrist point commonly used in treatment of chemical dependency: HT7, Sympathetic, LU, KI, LV, LI4 OR Acupuncture alone	30 mins, 5 treatments per week for 4 weeks	Educational smoking cessation program with sham acupuncture (Sham plus)	141 (38/45/58)	Smoking cessation (smoking or not) [BL to Mth 1, 3, 6, 12, 15, 18]	**Increased cessation** Mth 1: Acupuncture alone, +10%; Acupuncture plus, +40%; Sham plus, +22%; Between group, p=0.023

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Percentage decrease in cigarettes smoked [BL to Mth 1, 3, 6, 12, 15, 18]	**Reduced smoking** Mth 1: Acupuncture alone, -49%; Acupuncture plus, -53%; Sham plus, 40%; Between group, p=0.003
							Craving intensity [BL to Mth 1, 3, 6, 12, 15, 18]	NS
							Beck Depression Inventory [BL to Mth 1, 3, 6, 12, 15, 18]	NS
							Zung Anxiety Scale [BL to Mth 1, 3, 6, 12, 15, 18]	NS
Bradbury, et al. (2017) [Australia, WPRO] [46]	Randomized controlled trial	Chronic psychological stress	Omega-3 Fish Oil	12 weeks: Fish oil 4000mg as 2.2 g EPA, and 0.44 g DHA per day.	Placebo	90 (45/45)	Perceived Stress Scale [BL to Wk 12]	NS
							Omega-3 index [BL to Wk 12]	**Improved omega-3 fatty acids** Arachidonic acid (AA): Fish oil -22.6; Placebo -11.5 Between group (-8.7, p=0.002) EPA: Fish oil +7.3; Placebo -0.5; Between group (+9.6, p<0.001) DHA: NS AA: EPA (%): Fish oil -13.5; Placebo -0.8; Between group (-13.0, p<0.001) EPA: AA (%): Fish oil +0.28; Placebo +0.2; Between group (+3.0, p<0.001)

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Plasma interleukin-1β [BL to Wk 12]	NS
							Plasma interleukin-6 [BL to Wk 12]	NS
							Plasma interleukin-10 [BL to Wk 12]	NS
							Tumor necrosis factor-α [BL to Wk 12]	NS
							High-sensitivity c-reactive protein [BL to Wk 12]	NS
							Salivary cortisol/DHEA ratio [BL to Wk 12]	NS
							Depression, Anxiety, Stress Scale [BL to Wk 12]	NS
							Occupational Stress Inventory Strain and Resources subscales [BL to Wk 12]	NS
							COPE Inventory [BL to Wk 12]	NS
							Copenhagen Burnout Inventory [BL to Wk 12]	NS
Breed and Bereznay (2017) [USA, AMRO] [41]	Uncontrolled trial	Bipolar Disorder (patients with PHQ-9 scores ⩾ 10 or GAD-7 scores ⩾ 10	Individualized naturopathic care consisting of nutraceuticals, pharmaceuticals, homeopathics, and/or herbal medicines	At least 2 community health centre visits over 26 months, mean number of visits 3.3	Nil	60	Patient Health Questionnaire [Group average #, initial to final]	**Increased quality of life** -7.8, (p<0.0001) >50% improvement: 58.6%
							Generalized Anxiety Disorder 7-item scale [Group average #, initial to final]	**Reduced anxiety symptoms** -5.2, (p<0.0001) >50% improvement: 50%
Calabrese, et al. (2008) [USA, AMRO] [25]	Randomized controlled trial	Anxiety and depression (⩾65 yrs, without signs of dementia)	*Bacopa monnieri* aerial parts dry methanol extract tablet, standardized to 50% bacosides A and B	300mg BID, 12 weeks (6 wk placebo run-in)	Placebo	48 (24/24)	Rey Auditory Verbal Learning Test delayed recall (# of words) [BL to Wk 6 and 12]	**Increased verbal learning** Wk 6 (+0.2 vs -0.2) Wk 12 (+1.2 vs +.01) (p=0.03)

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Rey Auditory Verbal Learning immediate reaction times [BL to Wk 6 and 12]	NS
							Center for Epidemiologic Studies Depression scale [BL to Wk 6 and 12]	**Reduced depression** Wk 6: -0.1 vs +1.8 Wk 12: -0.9 vs +0.8, (p=0.05)
							State-Trait Anxiety Inventory [BL to Wk 6 and 12]	**Reduced anxiety** Wk 6, -2.0 vs +2.7 Wk 12, -1.6 vs +1.1, (p=0.04)
							Stroop task reaction time (seconds) [BL to Wk 6 and 12]	**Reduced task reaction time** Wk 6, -3.8 vs -0.6 Wk 12, -2.9 vs -0.4, (p=0.003)
							Stroop task errors (seconds) [BL to Wk 6 and 12]	NS
							Divided attention task score [BL to Wk 6 and 12]	NS
							Wechsler Intelligence Scale digit task [BL to Wk 6 and 12]	NS
							Profile of Mood States [BL to Wk 6 and 12]	NS
							Heart rate [bpm] [BL to Wk 6 and 12]	**Reduced heart rate** Wk 6, -1.4 vs +2.8 Wk 12, -1.1 vs +5.1, (p=0.01)
							Blood pressure [mmHg] [BL to Wk 6 and 12]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Cooley, et al. (2009) [Canada, AMRO] [34]	Randomized controlled trial	Anxiety	Naturopathic care- lifestyle and diet counseling, deep breathing techniques, herbal: *Withania somnifera 300mg BID*, multivitamin/ mineral formula.	Naturopathic Care once per week for 30 Min for 12 Weeks	Psychotherapy care: patient directed counseling, cognitive behavioral therapy, educated on healthy diet, reducing caffeine/tobacco stimulants, deep- breathing techniques, exercise advice, matched placebo supplement	75 (36/39)	The Fatigue Questionnaire [BL to Wk 12]	**Reduced fatigue** Subjective: NM, -20.39; PC, -2.38 Between group (-18.01, p<0.0001) Physical: NM, -14.29; PC, -1.10 Between group -13.19 (p=0.0033) Motivation: NM, -18.95; PC, +1.37 Between group -20.32 (p<0.0001) Concentration: NM, -1.98; PC, +0.37 Between group -17.51 (p<0.0001)
							Measure Yourself Medical Outcomes [BL to Wk 12]	**Reduced symptoms** Symptom 1: NM, -2.24; PC, -0.46 Between group -1.77 (p<0.0001) Symptom 2: NM, -1.94; PC, -0.86 Between group -1.08 (p=0.0115)
							Weight (kg) [BL to Wk 12]	**Reduced weight** -1.47 (p=0.00146)
							Body mass index (BMI) (kg/m2) [BL to Wk 12]	**Reduced BMI** -0.56 (p=0.00128)
Gangadhar, et al. (2013) [India, SEARO] [20]	Randomized controlled trial	Major depressive disorder (non-suicidal hospital out-patients)	Group 1: Generic yoga module of *asana* poses and breathing procedures from traditional texts Group 2: Combination yoga + medication	1hr daily for 2 wks, then weekly for 2 wks, then monthly for 2 months, with optional home practice	Psychiatrist-prescribed antidepressant medication	58 (15/27/ 16)	Hamilton Depression Rating Scale [BL to Mth 1 and 3]	**Reduced depression** Mth 1: Yoga only, -12.5; Yoga+medication, -10.00; Medication only, -7.1; Between group p=0.029 Mth 3: Yoga only, -14.9; Yoga+medication, -12.7; Medication only, -9.0; Between group p=0.001

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Clinical Global Impression Scale (CGI) – Depression Severity [BL to Mth 1 and 3]	**Reduced depression severity** Mth 1: Yoga only, -2.2; Yoga + medication, -1.7; Medication only, -0.9; Between group p=0.001 Mth 3: Yoga only, -2.9; Yoga + medication, -2.5; Medication only, -1.6; Between group p=0.001
							CGI – Depression Improvement (lower score represents greater improvement) [BL to Mth 1 and 3]	**Reduced symptoms** Mth 3: Yoga only, -0.6; Yoga + medication, -0.7; Medication only, -0.6; Between group p=0.001
							Responders/Remitters (no. of participants) [BL to Mth 1 and 3]	**Increased response to treatment** Mth 1: Yoga only +11; Yoga + medication +11; Medication only +2; Between group p=0.003 Mth 3: Yoga only +14; Yoga + medication +22; Medication only +5; Between group p=0.001
Govindaraj, et al. (2018) [India, SEARO] [39]	Uncontrolled trial	Schizophrenia (stabilized patients on antipsychotic medications)	Yoga: *asana* postures, *pranayama* breathing, and OM chanting	20 sessions, 1-hour in length, over 6 weeks	Nil	15	Scale for Assessment of Negative Symptoms (of schizophrenia) [BL to 1 Mth]	**Reduced symptoms** -30.36, ($p<0.001$)
							Scale for Assessment of Positive Symptoms (of schizophrenia) [BL to 1 Mth]	**Reduced symptoms** -21.34, ($p<0.001$)
							Socio-occupational dysfunction – Groningen Social Disability Scale [BL to 1 Mth]	**Reduced dysfunction** -25.01, ($p<0.001$)

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Social cognition – Social Cognition Rating Tool for Indian Setting [BL to 1 Mth]	**Increased social cognition** +18.97, (p<0.001)
Katzman, et al. (2007) [Canada, AMRO] [31]	Case report	Social anxiety disorder (adults taking Quetiapine)	Self-prescribed supplement, abs+ (containing 270mg green-tea-derived epigallocatechin-gallate (EGCG) and 3,400mg conjugated linoleic acid (CLA))	Daily administration of abs+ for 10-24 weeks	Nil	4	Total weight, body fat percentage (BF%), body fat mass (BFM) and lean body mass (LBM) [pre- and post- intervention]	**Improved anthropometrics** **Increase** total body weight in two, no change in one, **Reduced** in one **Reduced** BFM, BF% in all. **Increased** LBM in all.
Leung, et al. (2018) [Canada, AMRO] [36]	Randomized controlled trial (pilot)	Anxiety (children and adolescents)	Acupuncture and cupping and/or ear seeds. examples of points included: LI4, Du20, He7, Pe6, CV4, CV6, CV, AB14, B15, Du4, TW5, Yin Tang, CV12, Sp6, St36, Sp20, Ki3, Ki7, B23 and B25	5 sessions, 30 minutes 1 per week for 5 weeks	Waitlist control	19 (10/9)	Hamilton Anxiety Rating Scale [BL to Wk 5]	**Reduced anxiety** Acupuncture: -11.1 (p<0.001); Waitlist Control: NS Waitlist post-treatment: +10.38 (p=0.007); Between group at endpoint: NS
							Multidimensional Anxiety Scale for Children (MASC-2) [BL to Wk 5]	**Reduced anxiety** Acupuncture: NS; Waitlist control: NS Waitlist post-treatment: -8.37 (p=0.022) Between group at endpoint: NS
							MASC-Parent [BL to Wk 5]	**Reduced patient-reported anxiety** Acupuncture: -9.5 (p=0.008); Waitlist: NS Waitlist post treatment: -5.13 (p=0.048) Between group at endpoint: Acupuncture -15.4, (p=0.025)

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Manocha, et al. (2011) [Australia, WPRO] [24]	Randomized controlled trial	Stress, anxiety and depressed mood (full time workers)	"Mental silence" Meditation (Sahaja yoga)	Twice weekly 1-hour sessions plus twice daily 10 – 20-minute practice at home for 8 weeks	Relaxation active control vs wait-list (no treatment) control	178 (59/56/ 63)	Psychological Strain Questionnaire [BL to Wk 8]	**Reduced psychological strain** Meditation -37.0; Relaxation -22.30 Waitlist-17.5 (p=0.026)
							State/Trait Anxiety Inventory for Adults [BL to Wk 8]	NS
							Profile of Mood States, Depression-dejection subscale [BL to Wk 8]	**Reduced depression** Meditation -3.0; Relaxation: NS No treatment: NS (p=0.019)
Naveen, et al. (2013) [India, SEARO] [21]	Randomized controlled trial	Depression (non-suicidal adult outpatients)	Yoga therapy module developed for patients with depression: *asana* postures, stretching, *pranayama* breathing, chanting, yogic counselling	(60 min, daily for 10 days, then weekly for 2 wks, booster class at Wk 12, and home practice)	Yoga with anti-depressant medication, Anti-depressant medication alone.	137 (23/36/ 78)	Hamilton Depression Rating Scale [BL to Wk 12]	**Reduced depression** Yoga only, -14.0; Yoga and medication, -13.5; Medication only, -8.3 Between group p=0.005
							Clinical Global Impression (of depression severity) [BL to Wk 12]	**Reduced depression** Yoga only, -2.8; Yoga and medication, -2.7; Medication only, -1.9 Between group: p=0.001
							Brain-derived neurotrophic factor, serum (ng/mL) [BL to Wk 12]	**Increased brain-derived neurotrophic factor** Yoga only, +1.1; Yoga and medication, +1.9; Medication only, +2.1 Between group p=0.02

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Naveen, et al. (2016) [India, SEARO] [22]	Randomized controlled trial	Major depression (non-suicidal adults)	Yoga therapy module developed for patients with depression: *asana* postures, stretching, *pranayama* breathing, chanting, yogic counselling	(60 min, daily for 10 days, then weekly for 2 wks, booster classes Mths 2 and 3, home practice)	Yoga with anti-depressant medication, Anti-depressant medication alone.	54 (19/19/16)	Cortisol, serum (reduction vs. increase) [BL to Wk 12]	**Reduced cortisol** Yoga only, 68.4%; Yoga and medication, 68.4%; Medication only, 31.3% Between group p=0.042
							Brain-derived neurotrophic factor (BDNF), serum (ng/mL) [BL to Wk 12]	**Increased with lower cortisol** Negative correlation between change in BDNF and change in cortisol. Yoga only p=0.008, Yoga and medication NS, Medication only NS
Ross, et al. (2008) [USA, AMRO] [42]	Retrospective cohort study	Eating disorders	Various integrative therapies for insomnia and constipation: insomnia was treated with instructions on sleep hygiene as well as an herbal product (containing valerian root extract, *Rhodiola rosea* root extract, Hops strobiles extract, *Passiflora incarnata* aerial parts extract, and German chamomile flower extract) and/or 5-hydroxy-tryptophan (the metabolic precursor to serotonin) were prescribed. Constipation was treated with plant-based digestive enzymes at mealtimes and a daily probiotic supplement containing *Lactobacillus rhamnosus*	2 or 3 days	Usual care	65 (27/38)	Medications used for sleep [After Dy 3]	NS
							Sleep medications [After Dy 3]	NS
							Constipation medications [After Dy 3]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sarris, et al. (2009) [Australia, WPRO] [28]	Randomized controlled trial	Generalized anxiety (adults (18-65 years with > 1 month of > 10 on Beck Anxiety Inventory)	Tablet from pressed, dried aqueous extract of *Piper methysticum* (Kava) standardized to 50mg kavalactones per tablet	5 Kava tablets (total 250mg of kavalactones/day) for 3 weeks	Placebo	60	Hamilton Anxiety Scale (HAM-A) [BL to Wk 1 and phase 1 and 2]	**Reduced anxiety** Phase 1: −9.9 vs −0.8, (p<0.0001) Phase 2; −10.3 vs. +3.3, (p<0.0001) Increased pooled effect in kava across phases (p<0.0001)
							Beck Anxiety Inventory (BAI) [BL to Wk 1 and post treatment 1 and 2]	**Reduced anxiety** Phase 1: −7.2 vs −1.6, (p=0.001) Phase 2: −8.1 vs. +1.4, (p=0.001) Increased pooled effect in kava (p=0.001)
							Montgomery-Asberg Depression Rating Scale (MADRS) [BL to Wk 1 and post treatment 1 and 2]	**Reduced depression** Phase 1: −5.9 vs −1.1, (p=0.003) Phase 2: −7.6 vs. +3.3, (p=0.003)
Sarris, et al. (2009) [Australia, WPRO] [26]	Randomized controlled trial (cross-over)	Adults (age 18-65) with Massive Depressive Disorder and comorbid anxiety (minimum score of 10 on Beck Anxiety Inventory)	*Hypericum perforatum* (St. John's wort (SJW) 1.8g (standardized 990mcg of hypericin, and 1500 mcg of flavone glycoside) and *Piper methysticum* (Kava) 2.66g (standardized to 50 mg of kavalactones)	8 weeks: SJW 1 tablet TID Kava 1 table TID	placebo	28	Beck Depression Inventory (BDI-II) [Wk 2 to Wk 6 and 10]	**Reduced depression** Intention-to-treat Over time: p=0.047 Between group: p=0.023 Completer analyses Over time: p=0.008 Between group: p=0.003
							Beck Anxiety Inventory [Wk 2 to Wk 6 and 10]	NS
							WHO Quality of Life Survey (WHOQOL) [Wk 2 to Wk 6 and 10]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sarris, et al. (2012) [Australia, WPRO] [29]	Randomized controlled trial	Mild to moderate anxiety (adults (18-65 years) with HAM-A score between 14 and 25)	Three-arm study design: kava vs oxazepam vs placebo, each arm contained 3 tablets and 1 capsule of either active ingredient or identical placebo *Piper methysticum* (Kava) acute dose of 180mg kavalactones vs 30mg oxazepam after exposure to cognitive tasks	Single dose of each intervention 1 week apart over 3 weeks	Placebo	22	State – Trait Anxiety Inventory-State (STAI-S) [BL to visit 2 and 3]	Significant interaction between conditions after exposure to cognitive tasks (p=0.046) Oxazepam: -2.6, (p=0.035) Placebo: +1.8, (p=0.08) Kava: NS
							Bond-lader VAS [BL to visit 2 and 3]	Oxazepam: 'calmness': +10.25, (p-0.02) 'alertness': -13.45, (p=0.032)
							STCI-S [BL to visit 2 and 3]	Placebo: Seriousness, -1.5 (p=0.047) placebo -1.32, (p=0.036) Oxazepam: 'bad mood' -1.14, (p<0.01)
							Post-Intervention Cognitive Deficits	Oxazepam: 'alertness' (p<0.001)
Sarris, et al. (2012) [Australia, WPRO] [27]	Randomized controlled trial	Major Depressive Disorder (adults)	*Hypericum perforatum* (St John's wort) vs Sertraline	26 Weeks: SJW (LI-160, 900 – 1 500 mg, standardized for between 0.12 – 0.28 % hypericin) vs Sertraline (50 – 100 mg) vs placebo. All taken TID. SJW and Sertraline dose titrated according to response throughout trial	Placebo: matched to both active interventions	124 (35/49/ 40)	Hamilton depression rating scale (HAM-D) [Wk 10 to 26]	NS
							Beck Depression inventory (BD) and improvement (CGI-I) [Wk 10 to 26]	NS
							Global Assessment of Functioning (GAF) [Wk 10 to 26]	NS
							Clinical Global Impressions Scales for severity (CGI-S) [Wk 10 to 26]	NS
							Clinical Global Impressions Scales for severity (CGI-S) and improvement (CGI-I) [Wk 10 to 26]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sarris, et al. (2013) [Australia, WPRO] [30]	Randomized controlled trial	Generalized Anxiety Disorder without Major Depressive Disorder (adults (age 18-65) with DSM-IV diagnosed MADRS > 17)	Aqueous extract of *Piper methysticum* (Kava)	6 weeks: 120mg Kavalactones OD (one 3 g tablet BID) for the first 3-week controlled phase, titrated to 240 mg of kavalactones in non-responders at the 3-week mark for the second 3-week controlled phase.	Placebo	Phase 1: 58 (29/29) Phase 2: 29 (13/16)	Hamilton Anxiety Rating Scale (HAM-A) [BL to Wk 6]	**Reduced anxiety** −7.6 points vs −4.2, (p=0.046). Effect more pronounced in those with moderate to severe pre-intervention anxiety (no other comorbid anxiety disorders) (p=0.020)
							Genetic polymorphisms assessed for improved response to Kava [BL to Wk 6]	GABA transporter polymorphisms rs2601126 (p=0.021) and rs2697153 (p=0.046) were found to be associated with greater HAM-A reduction in Kava group
							Beck Anxiety Inventory (BAI) [BL to Wk 6]	NS
Sarris, et al. (2014) [Australia, WPRO] [15]	Secondary analysis (sub-cohort from PMID: 2450-0245)	Major depressive disorder (adults score of > 25 on Inventory of Depressive Symptomatology – Clinician-Rated)	S-adenosylmethionine (SAMe) vs escitalopram	12 Weeks: SAMe 1600-3200 mg/day; escitalopram 10mg/day	Placebo	102 (32/35/35)	Hamilton Depression score (HAM-D) [BL to Wk 12]	**Reduced depression** SAMe -7.31; Escitalopram -6.69; placebo -4.00 (p=0.039) Between group (SAMe vs placebo, p=0.018)
							Response rates (HAM-D >50% reduction) [BL to Wk 12]	**Increased response** SAMe 45% Escitalopram 31% Placebo 26%
							Remission rates (<7) HAM-D [BL to Wk 12]	**Increased remission** SAMe, 34%; Escitalopram, 23%; Placebo, 6% (p=0.014) Between group (SAMe vs placebo, p=0.003)
							Correlation of BL histamine and carnitine levels with HAMD-17	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Sarris, et al. (2015) [Australia, WPRO] [16]	Secondary analysis (PMID: 2450-0245)					113 (62 Female/ 51 Male)	Hamilton Depression Rating Scale (HAM-D) [BL to Wk 12]	**Reduced in males** **Reduced** between SAMe to placebo for males (not females) (-8.9 vs -4.6, p= 0.034) NS difference between gender groups.
Sarris, et al. (2015) [Australia, WPRO] [37]	Randomized controlled trial	DSM-5-diagnosed obsessive-compulsive disorder (OCD) participants (18 – 70 years)	N-acetyl cysteine (NAC)	16 weeks: Week 1 1000mg Week 2 2000mg Week 3 3000mg	placebo	35 (20/15)	Yale – Brown Obsessive Compulsive Scale (YBOCS) [BL to Wk 4, 8, 12 and 16]	**Reduction in compulsion** Wk 12: NAC, (p=0.013) Wk 16: NAC, NS
							HAM-A [BL to Wk 4, 8, 12 and 16]	NS
							MADRS [BL to Wk 4, 8, 12 and 16]	NS
							CSG-S/I [BL to Wk 4, 8, 12 and 16]	NS
							General health (GHQ-28) [BL to Wk 4, 8, 12 and 16]	NS
Sarris, et al. (2016) [Australia, WPRO] [38]	Secondary analysis						Age (years), OCD severity (YBOCS total at baseline), duration of illness (years), gender, medication status, and OCD symptom presentation [BL to Wk 4, 8, 12 and 16]	Significant effect age (<34 p=0.037. remained with OCD severity as covariate (p-0.044) Significant effect for <34 less than 17year OCD duration (p=0.037)
Sarris, et al. (2019) [Australia, WPRO] [32]	Randomized controlled trial	Generalized Anxiety Disorder (GAD) (18-75 years; primary diagnosis of GAD at study entry (DSM-V; confirmed via the MINI International	L-theanine	10 Weeks Phase 1 450 mg of L-theanine first 4 weeks, titrated to 900 mg of L-theanine in minimal responders (<35% reduction in HAM-A) at	Placebo	46 (22/24)	Hamilton Anxiety Rate Score [BL to Wk 10]	NS
							Insomnia Severity Index [BL to Wk 10]	**Improved sleep for individuals with clinical insomnia** Between group: NS Participants without clinical insomnia: **Increased** self-reported sleep satisfaction (p=0.015)

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
		Neuro-psychiatric Interview version 6.0 and Hamilton Anxiety Rating Scale [HAMA] score ⩾16)		the 4-week mark for the second 4-week controlled Phase (phase 2)				**Reduced** difficulty falling asleep (p=0.049) problems waking up early (p=0.017) increased self-reported sleep satisfaction (p<0.001)
Sarris et al. (2018) [Australia, WPRO] [17]	Randomized controlled trial	Major Depressive Disorder (18-75 DSM-5 diagnostic criteria, currently taking an SSRI, SNRI, NaRI, tetracyclic (mirtazapine) or 5-HT2c antagonist (agomelatine) for a minimum of four weeks)	S-adenosylmethionine (SAMe); Folinic acid and co-factor vitamin B12	8 Weeks: SAMe (800 mg/day); Folinic acid (500 mcg/day) and Vitamin B12 (200 mcg/day), given in divided doses twice daily	Placebo	107 (55/52)	Montgomery-Asberg Depression Rating Scale [BL to Wk 8]	NS
							Beck Depression Inventory-II [BL to Wk 8]	NS
							Hamilton Anxiety Rating Scale [BL to Wk 8]	NS
							Short Form-12 [BL to Wk 8]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 8]	NS
							Clinical Global Impression Severity and Improvement (CGI-S, CGI-I) [BL to Wk 8]	NS
Sarris, et al. (2019) [Australia, WPRO] [18]	Randomized controlled trial	Major Depressive Disorder (18-70 DSM-5 diagnostic criteria, currently taking an SSRI, SNRI, NaRI, tetracyclic (mirtazapine) or 5-HT2c antagonist (agomelatine) for a minimum of four weeks)	Nutraceutical combination: SAMe, folinic acid, vitamin B12. Capsules: omega-3 fatty acid concentrate, 5-Hydroxy tryptophan, zinc picolinate, vitamin B6, vitamin C, magnesium (amino acid chelate, elemental, vitamin E	8 weeks: SAMe (800 mg/day) Folinic acid (500mcg/day) Vitamin B12 (200mcg/day) Omega-3 fatty acid concentrate (EPA-esters 1000 mg/day, DHA-esters 656 mg/day)	Placebo	158 (81/77)	Montgomery-Asberg Depression Rating Scale [BL to Wk 8]	NS
							Beck Depression Inventory II [BL to Wk 8]	NS
							Hamilton Anxiety Rating Scale [BL to Wk 8]	NS
							SF-12 -Short Form Survey-12 [BL to Wk 8]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 8]	NS
							Arizona Sexual Experience Questionnaire [BL to Wk 8]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
				5-HTP (200 mg/day) Zinc picolinate (30 mg elemental/ day) Vitamin B6 (100 mg/day) Vitamin C (60 mg/day) Magnesium (amino acid chelate, elemental 40 mg/day) Vitamin E (40IU/day)			CORE Assessment of Psychomotor Change [BL to Wk 8]	NS
							Clinical Global Impression (CGI) [BL to Wk 8]	NS
							CGI-S [BL to Wk 8]	NS
							CGI-I [BL to Wk 8]	NS
							The Systematic Assessment for Treatment Emergent Effects [BL to Wk 8]	NS
							The Sternbach and Hunter Serotonin Toxicity Criteria [BL to Wk 8]	NS
Scholey, et al. (2017) [Australia, WPRO] [44]	Randomized controlled trial	Sleep difficulties	Multi vitamin / herbal combination: Lactium™ (hydrolysed milk protein; alpha casozepine enriched) 75 mg; Sour date (Zizyphus jujube var. spinosa) ext. equiv. to dry seed 4.5 g; Hops (Humulus lupulus) ext. equiv. to dry flower 500 mg; Magnesium oxide (equivalent magnesium) 81.7 mg (52.5 mg); Vitamin B6; pyridoxine hydrochloride (equivalent pyridoxine) 10 mg (8.23 mg)	3 Weeks (includes 1 week single-blind placebo run-in) 2 tablets 30 min before sleep	Placebo	171 (85/86)	Pittsburgh Sleep Quality Index (PSQI) [BL to Wk 3]	NS
							Leeds Sleep Evaluation Questionnaire [BL to Wk 3]	NS
							Epworth Sleepiness Scale [BL to Wk 3]	NS
							Insomnia Severity Index [BL to Wk 3]	NS
							Consensus Sleep Diary [BL to Wk 3]	NS
							Burckhardt Quality of Life Scale [BL to Wk 3]	NS
							Chalder Fatigue Scale [BL to Wk 3]	NS
							Bond-Lader Visual Analogue Scale [BL to Wk 3]	NS
							State-Trait Anxiety Inventory State subscale [BL to Wk 3]	NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Stress and Fatigue Visual Analogue Mood Scales [BL to Wk 3]	NS
							Multi-tasking Framework [BL to Wk 3]	NS
Smith, et al. (2018) [Australia, WPRO] [19]	Uncontrolled trial	Major Depressive Disorder	Docosahexaenoic acid (DHA)	8 weeks: Low-dose DHA, (260 mg or 520 mg/day)	Nil	26	Hamilton Depression Rating Scale [BL to Wk 8]	**Reduced depression** -10.33, ($p<0.001$)
							⩾50% reduction on HAM-D [BL to Wk 8]	**Increased clinical response** Clinical response to treatment: 54% In remission: 46% ($p<0.0001$)
							Clinical Global Impression Severity Scale [BL to Wk 8]	**Reduced overall symptoms** -1.28, ($p<0.05$)
							Epsworth sleepiness scale [BL to Wk 8]	NS
Thirthalli, et al. (2013) [India, SEARO] [23]	Non- Randomized controlled trial	Major depression (hospital outpatients)	Yoga, combination yoga and anti-depression medication	*Yoga:* daily 1 hour yoga sessions for 2 weeks, then once/week check in yoga sessions for 2 weeks, then once/month for 2 months plus encouragement to practice at home. Anti-depressant medication: Either Fluoxetine (20-40 mg/day),	Anti-depressant medication: Either Fluoxetine (20-40 mg/day), Escitalopram (10-15 mg/day), Sertraline (50-100 mg/day) or Mirtazapine (15-30 mg/day) as prescribed by psychiatrist. Healthy hospital staff controls on no medication	72 (19/19/16/18)	Serum cortisol [BL to Mth 3]	**Reduced cortisol** Yoga groups $p=0.006$ Medication alone group NS Control group NS
							Hamilton Depression Rating Scale [BL to Mth 3]	**Direct correlation between reduction in depression and reduction in cortisol** Treatment groups total $p=0.001$ Yoga alone $p=0.008$ Yoga and medication NS Medication alone NS Control group NS

Author (year) [Country World, Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
				Escitalopram (10-15 mg/ day), Sertraline (50-100 mg/day) or Mirtazapine (15-30 mg/day) as prescribed by psychiatrist				
Usher, et al. (2019) [USA, AMRO] [40]	Non-randomized controlled trial	Psychotic episode (Age 15 to 25y, early Assessment and Support Alliance client or graduate (within past 2 years).	Holistic behavior intervention models to facilitate healthier living (M^3) (mindfulness meditation, cooking classes, field trips to a supermarket and a low-cost fast-food restaurant for hands-on learning, nutrition education, exercise, and moderated group discussion.	6 weeks: 6 sessions	Control (usual care)	33 (17/16)	Session attendance (target of ⩾50% of enrolled participants attending at least 4 out of 6 sessions) [BL to Wk 12]	Outcome met (88% completion rate of 4 or more sessions [mean 4.29, SD 1.26]).
							Anthropometric [BL to Wk 12]	NS
							Quick Scale for the Assessment of Negative – Positive Symptoms (QSANS-QSAPS) [BL to Wk 12]	**Increased negative symptoms** Behavior: Increased negative, t= -3.29 (p=0.02) Psychotropic medication: Increased positive, t=−3.10 (p = 0.004)
							Child and Youth Resilience Measure (CYRM) [BL to Wk 12]	Not reported
							Short Form Health Survey (SF-12) [BL to Wk 12]	Not reported
Zick, et al. (2011) [USA, AMRO] [45]	Randomized controlled trial	Insomnia for ⩾ 6-months	German chamomile *(Matricaria recutita)*	28 Days: 270 mg of chamomile twice daily	Placebo	34 (17/17)	Total sleep time (hrs) [BL to Dy 90]	NS
							Subjective sleep efficiency	NS
							Beck Depression Inventory	NS
							State Trait Anxiety Inventory – Trait Subscale	NS
							Fatigue Severity Scale	NS

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23 Musculoskeletal Conditions

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HIGHLIGHTS

- Musculoskeletal (MSK) conditions are seen in all age groups and are becoming a significant disease burden globally.
- The main MSK conditions that patients seeking naturopathic care present with include chronic pain, low back pain, injury related symptoms, osteoarthritis, fibromyalgia and sciatica.
- Naturopaths/NDs approach to MSK conditions employs a range of internal and external therapies and focuses on both the physical and psychological aspects for each patient.
- 89.3% of the research on naturopathic interventions for the treatment of MSK conditions indicated a positive outcome.

Musculoskeletal conditions represent a significant and growing disease burden globally, with increases observed across all regions, all age groups, and all income levels [1]. The musculoskeletal system is integral to good health and can include more than 150 diagnoses that affect the locomotor system. The musculoskeletal system provides form, stability and movement to the human body. It consists of the bones, muscles, tendons, ligaments, joints, cartilages, and connective tissues of the body but its central role can also pose major threats to health by limiting physical and mental capacities and functional ability [2]. The symptoms and conditions of the musculoskeletal system can be grouped into general or unspecific symptoms (e.g., pain, muscle cramps or spasms), arthritic or rheumatic conditions (e.g., gout, osteoarthritis, rheumatoid arthritis, fibromyalgia), joint or ligament injuries or disorders (e.g., bursitis, tendonitis, sciatica, plantar fasciitis, sprains, strains, carpal tunnel syndrome), bone disorders (e.g., osteopenia or osteoporosis) and other conditions (e.g., connective tissue disorders).

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=30) naturopathic researchers undertook in the field of musculoskeletal conditions. This research includes a total of 2,243 participants and was conducted in Germany (n=18), the United States of America (USA) (n=4), Australia (n=4), India (n=3) and Canada (n=2). The study designs include randomized control trials (n=26), uncontrolled trials (n=2), secondary analysis (n=2) and follow-up (n=1). The studied interventions featured a varying range of therapeutics including cupping (n=6), acupuncture (n=4), bodywork such as cranial sacral therapy (CST), *Gua Sha* therapy, *tai chi* and massage (n=4), yoga (n=4), clinical nutrition (n=3), hydrotherapy (n=3), complex naturopathic care (n=3), herbal medicine (n=2), dental (n=1) and Intravenous therapy (n=1).

The musculoskeletal conditions examined in these studies include chronic neck pain (n=13), osteoarthritis of the knee or hip (n=6), low back pain (n=3), fibromyalgia (n=2), heel pain (n=1), tendonitis (n=1), heel pain (n=1) and temporomandibular joint pain (n=2). Of all the naturopathic clinical studies examining musculoskeletal condition populations, 89.3% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 23.1: Clinical research investigating musculoskeletal conditions conducted by naturopathic researchers*. This body of naturopathic research on musculoskeletal conditions is also supported by over 50 observational studies and more than 50 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Naturopathic research demonstrates that patients who pursue naturopathic care for musculoskeletal conditions may benefit from naturopathic interventions. Musculoskeletal treatment was among the first clinical area for which naturopathic care gained prominence among the global population [3], and an international cross-sectional survey of naturopathic practice found that musculoskeletal conditions are the most common reason for patients to seek naturopathic treatment

[4]. Common musculoskeletal complaints identified in an international cross-sectional naturopathic survey included chronic pain, injury-related symptoms, osteoarthritis, fibromyalgia, and sciatica [4]. The inter-systems and holistic nature of naturopathic treatment lends itself well to treatment and management of musculoskeletal conditions, which are not only characterized by pain and reduced physical function of the musculoskeletal system itself, but can also lead to significant mental health decline, increased risk of developing other chronic health conditions and increased all-cause mortality [5]. Naturopathic treatment approaches varied widely, both in the cross-sectional survey and in the published literature reviewed below, which indicated the diverse and individualized naturopathic approach taken with patients presenting with musculoskeletal concerns.

The variety of naturopathic physical modalities studied by naturopathic physicians shows a diverse set of therapeutic tools, which is influenced by the long-standing historical focus of naturopathic care on musculoskeletal health [3]. As non-pharmacological approaches to treatment of musculoskeletal conditions become prioritized in primary health care [6], naturopaths/naturopathic doctors may be well-placed to play a greater role in integrative and multi-disciplinary models of musculoskeletal care. Musculoskeletal conditions are also one of the few areas where whole practice naturopathic care has demonstrable effectiveness as an intervention in multiple randomized controlled trials [7, 8], which suggests a larger primary care role for naturopaths/naturopathic doctors in this area. This holistic approach of naturopathic practice may be particularly important for patients who seek its care to treat musculoskeletal conditions, given that musculoskeletal conditions are also strongly associated with other elements of physical and mental health, and share many of the same preventable risk factors as other chronic conditions [5].

The increase in musculoskeletal conditions posing major threats to healthy ageing by limiting physical and mental capacities and functional ability [9], with profound consequences on an individual's ability to participate in social roles and in the prosperity of communities. While the contribution of musculoskeletal pain conditions to the global burden of disability has been widely acknowledged, this has largely not translated into global health policy initiatives [10]. There is a mismatch between the burden of musculoskeletal pain conditions and appropriate health policy response and planning internationally that can be addressed with an integrated research and policy agenda. Given the high levels of utilization of naturopathic care for musculoskeletal conditions, the historical focus of the naturopathic profession on musculoskeletal care, the holistic and inter-systems approach to naturopathic treatment that can address the whole person, and the active research presence of the naturopathic community in musculoskeletal research, naturopaths/naturopathic doctors should be considered in future policy responses to reducing the burden of musculoskeletal conditions.

Studies based on specific conditions:

Chronic Neck Pain

Fifteen studies investigated interventions on neck pain [11-25]. Six of those studies investigated different cupping treatments [11, 18-21, 25] and two investigated different acupuncture or acupressure protocols [17, 24]. Additional studies investigated thermotherapy [12], craniosacral therapy [16], Tai Chi [22], and yoga [13-15, 23].

Clinical finding

Cupping therapy may reduce neck pain, including pain at rest, movement-related pain, and neck disability while increasing quality of life in individuals with chronic non-specific neck pain. Cupping may also reduce pain in individuals with fibromyalgia.

A randomized controlled trial conducted in Germany investigated dry cupping for chronic non-specific neck pain [18]. Participants (n=25) received 5 treatments over two weeks and were compared to a waitlist group (n=25). Based on the Visual Analog Scale the treatment group experienced reduced pain at rest (cupping -19.4 vs waitlist +4.8; between groups -22.5, p=00002) and reduced movement-related pain (cupping -33 vs waitlist -12.9; between groups -17.8, p=0.01). There was a reduction in neck disability based on the Neck Disability Index (cupping -6.4; waitlist +0.1; between groups -6.3, p=0.002). An increase in quality of life, based on the Short Form 36 Questionnaire (SF-36), was reported on the scales related to bodily pain (between groups +13.8, p=0.006), vitality (between groups +10.2, p=0.006), social function (between groups +5, p=0.06) and mental health (between groups +11.4, p=0.04). A similar randomized controlled trial study from Germany (n=50) also investigated cupping for chronic neck pain delivered twice a week for three weeks (total of five treatments) with similar findings [25].

A randomized controlled trial conducted in India (n=60) investigated the addition of hot sand fomentation to an integrated treatment including yoga, a low fat and low salt vegetarian diet and sesame seed oil topical application over a five-day intervention [23]. The group that included the hot sand fomentation (n=30) reported a reduction in pain based on the Visual Analogue Scale

(-5.18 to -1.54, p<0.00), a reduction in neck disability (-23.27 to -11.07, p<0.001) and an increase in quality of life based on the SF-36 on the social functioning (+26.5 vs +15.25, p<0.035) and pain scale (+28.25 vs +10.09, p<0.01).

Low Back Pain

Five studies (n=700) on low back pain [7, 17, 26-28] were conducted. The interventions covered naturopathic care [7], a comparison of yoga to physical therapy [28], acupuncture [27], *Gua Sha* Therapy [25] and home-based needle stimulation [17].

Clinical finding

Yoga practice involving relaxation exercises, pranayama (yogic breathing), discussion of yoga philosophy and at-home yoga practice may reduce back pain and use of pain medication in individuals with chronic low back pain.

A large randomized control trial (n=320) conducted in the USA compared yoga, physical therapy (PT) and education for the treatment of chronic low back pain [28]. The yoga intervention (n=137) included relaxation exercises, pranayama, discussion of yoga philosophy and was supplemented with at-home daily practice materials. Following initial program (week 1 – 12), participants were re-randomized to a structured yoga maintenance program (n=64) or no structured maintenance (n=64). The PT intervention (n=129) included specific exercises, or stabilization exercises which were supplemented with at-home daily exercises. At twelve-weeks, participants were re-randomized to a structured PT maintenance program (n=64) or no structured maintenance (n=64). The education group consisted of an educational pamphlet "The Back Pain Help Book" with assignment sheet. Based on the Modified Roland Morris Disability Questionnaire both yoga and PT resulted in >30% reduction in disability score compared to education-alone group (yoga vs education 3.1 [95% CI 1.6 to 6.2], PT vs education 2.0 [95% CI 1.0 to 4.0]) [28]. All group showed a reduction in back pain with the greatest decrease based on the Back Pain Intensity Score reported in the PT group (yoga, -1.7; PT, -2.3; education, -1.4). The reduction in self-reported pain medication use was highest when comparing yoga to education alone (0.36 [95% CI 0.17 to 0.78].

A randomized controlled trial conducted in Canada (n=75) compared generalized naturopathic medical care (NM) (n=39) to a standardized educational booklet on exercise and relaxation exercises (n=36) for chronic low back pain over a twelve-week period of time [7]. The naturopathic care consisted of acupuncture, breathing exercises, nutritional counselling and physical exercises. Participants in the NM group reported a greater reduction in low back pain compared to the control group (Oswestry Low Back Pain Disability Questionnaire [Oswestry]: -5.0, p<0.0001). They also reported an increased quality of life on a number of scales from the SF-36: physical component (+8.47, p<0.0001), mental component (+5.56, p<0.0045), physical functioning (+5.56, p<0.0033), physical role (+11.48, p<0.001), bodily pain (+10.83, p<0.0001), general health (+7.18, p=0.0002), social functioning (+10.57, p<0.0001), emotional role (+8.05, p=0.0090) and mental health (+7.44, p=0.0003). Based on the Roland Morris Disability Questionnaire the NM group reported a reduction in disability (-4.0) while the education-only group reported an increase (+2.0) (between group, p<0.0001). The NM group also reported a reduction in number of NSAID pills used per week (-1.0) compared to the education group (+1.3).

Clinical finding

Naturopathic care involving acupuncture, breathing exercises, nutritional counselling and physical exercises may reduce low back pain, disability and use of pain medication, while increasing quality of life in individuals with chronic low back pain.

Osteoarthritis

Five studies investigated treatment approaches to osteoarthritis of the knee [29-33], with one study including participants with osteoarthritis of the hip [34]. Two studies examined the effects of clinical nutrition interventions on knee [32] and knee and hip osteoarthritis [34]. One study examined the effect of cabbage leaf wraps on knee osteoarthritis [31], while another investigated Swedish massage therapy [33].

The randomized controlled trial conducted in the USA on Swedish massage therapy investigated optimal treatment frequency strategies for knee osteoarthritis compared to usual care in 125 individuals [33]. The four intervention arms included 25 participants each and compared 8 weeks of 30 minutes massage once per week, 4 weeks of 30 minutes massage twice per week, followed by 4 weeks of 30 minutes massage once per week, 8 weeks of 60 minutes massage once per week, and 4 weeks of 60 minutes massage twice per week followed by 4 weeks of 60 minutes massage once per week. The investigators found that the optimal treatment duration that produced significant reductions in pain was 60 minutes. All 60-minute treatment groups showed significant improvements in pain compared to usual care, indicating that once-weekly massages would be an effective dosing strategy for improving osteoarthritis knee pain.

A randomized controlled trial conducted in Germany (n=81) investigated the effects of cabbage leaf wrapping for two hours/day for 4 weeks on osteoarthritis of the knee compared to topically applied diclofenac gel and usual care [31]. Investigators found significant reductions in pain (-12.2 mm on a 100mm Visual Analog Scale, p = 0.033) when cabbage leaf wrapping was compared to usual care; however, this difference was not significant compared to the topical diclofenac group. At the 12-week follow-up, there were no significant differences in knee pain scores between any of the groups suggesting that the cabbage leaf wrapping was as effective as topical diclofenac prescription.

Clinical finding

Cabbage leaf wrap may be as effective as topical anti-inflammatory gel in reducing knee pain in individuals with knee osteoarthritis.

Fibromyalgia

Two studies investigated two different treatment approaches to fibromyalgia [35, 36]. A randomized controlled trial conducted in Germany investigated the effects of cupping therapy on participants with fibromyalgia (n = 141) [36]. Participants were randomized into three separate groups. Group one received five cupping sessions over eighteen days (n = 47). Group two received five sham cupping sessions over eighteen days (n = 48). Group three served as a waitlist control (n = 46). On day eighteen, participants in the intervention group reported a significant decrease in pain based on the Visual Analog Scale (-12.4 mm difference, $p < 0.001$) compared to the waitlist control group but not to the sham cupping group (-3.0 mm difference, p = 0.396).

Other Musculoskeletal Conditions

Other musculoskeletal conditions researched included heel pain [37], temporomandibular joint pain [38, 39] and rotator cuff tendonitis [8]. An Indian study on heel pain (n=20) compared complex hydrotherapy to standard naturopathic physical care [37]. The hydrotherapy included alternating compresses to the heels and partial or vibrational massage to the legs, along with hot foot baths and mud packs. Based on the Visual Analogue Scale both groups showed reduced pain and based on the FFI both showed increased function, yet the increase was more significant in the complex hydrotherapy group.

Clinical finding

Naturopathic care involving herbal medicine, nutritional supplements, and diet and lifestyle advice may reduce facial pain in individuals with temporomandibular joint pain.

A temporomandibular joint pain randomized controlled trial conducted in the USA (n=128) comparing three treatment style interventions: traditional Chinese Medicine (n=42) (acupuncture, herbal therapy, massage and relaxation tapes), naturopathic medicine (n=36) (herbal medicine, nutritional supplementation, nutritional and lifestyle advice, stress reduction advice) to specialty dental care (n=50) (education, bite splints, self-care counselling and pain management strategies) [38]. All groups resulted in a reduction in their worst facial pain, but the improvement was greatest in the naturopathic medicine group.

Clinical finding

Naturopathic care involving dietary counselling, acupuncture and nutritional supplements may reduce pain and disability and increase quality of life in individuals with rotator cuff tendonitis.

A randomized control trial conducted in Canada (n=85) compared complex naturopathic care to standardized physical exercise (PE) for participants with rotator cuff tendonitis. The naturopathic medical care (NM) included dietary counselling, standardized acupuncture, and nutritional supplementation with Phlogenzym (bromelain [90mg], trypsin [48 mg] and rutin [100 mg]). The intervention lasted twelve weeks and resulted in significant reductions in pain and disability based on the Shoulder Pain and Disability Index (NM, -42.34; PE -23.59; between groups, -29.66, $p<0.0001$), reduced pain based on the visual pain analog scale (-1.67, $p<0.0001$) and an increased quality of life on all domains on the SF-36.

Table 23.1 Clinical research investigating musculoskeletal conditions conducted by naturopathic researchers

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Ali, et al. (2009) [USA, AMRO] [35]	Randomized controlled trial	Fibromyalgia syndrome	Intravenous micronutrient therapy (Myers' Cocktail): Magnesium chloride hexa-hydrate, 20% (5mL); Calcium gluconate, 10%) (3mL); Hydroxyocobalamin, 1000u/mL (1mL); Pyridoxine hydrochloride, 100mg /mL (1mL); Dexpanthenol, 250mg /mL (1mL); B-complex 100 (1mL) containing thiamine HCl [100mg], riboflavin [2mg], pyridoxine HCl [2mg], panthenol [2mg], niacin-amide [100mg + 2% benxyl alcohol], vitamin C [5mL of 500mg/mL], 20mL of sterile H20	8 weeks (+ 4-week washout): one infusion per week	Placebo	35 (17/18)	Tender Point Index [BL to Wk 8]	NS
							Visual Analogue Scale [BL to Wk 8]	NS
							Fibromyalgia Impact Questionnaire [BL to Wk 8]	NS
							Beck Depression Inventory [BL to Wk 8]	NS
							Health Status Questionnaire [BL to Wk 8]	NS
Arankalle, et al. (2016) [India, SEARO] [37]	Randomized controlled trial	Heel pain	Alternating compresses (AC) to heels and partial or vibro massage to legs (Neutral Immersion Bath; Hot Foot Bath; Infrared Radiation; Neutral Immersion Bath; Mud Pack	6 days	Naturopathic physical care (NPC)	20 (10/10)	Visual Analogue Scale [BL to Dy 6]	**Reduced pain** AC: -1.48 (p<0.001) NPC: -1.0 (p<0.001) Between group: NS
							Foot Functional Index (FFI) [BL to Dy 6]	**Increased function** AC: -18.47 (p-0.001) NPC: -14.99 (p=0.005) Between group: p=0.007
Cramer et al. (2011) [Germany, EURO] [11]	Randomized controlled trial	Chronic non-specific neck pain	Pneumatic pulsation therapy: pulsating cupping applied to neck and shoulder areas where manual pressure and lifting of the skin caused the most discomfort (5 treatments over 2 wks)	2 weeks: 5 treatments	Standard care: self-directed standard medical care, including physiotherapy, sports activities, and analgesics as needed	50 (25/25)	Pain intensity (numerical rating scale) [BL to Wk 2.5]	**Reduced pain intensity** Acupuncture: -1.4; Standard care: +0.24 Between group: p=0.001
							Total pain at motion (Visual Analogue Scale) [BL to Wk 2.5]	**Reduced total pain at motion** Acupuncture: -8.1; Standard care: +4.1 Between group: p < 0.001
							Maximum pain at motion (Visual Analogue Scale) [BL to Wk 2.5]	**Reduced maximum pain at motion** Acupuncture: -2.5; Standard care: -0.26 Between group: p=0.004

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Functional disability (Neck Disability Index) [BL to Wk 2.5]	**Reduced functional disability** Acupuncture: -5.5; Standard care: -0.3 Between group: p=0.025
							Short Form-36 (SF-36) health survey – physical component [BL to Wk 2.5]	**Increased physical function** Acupuncture: +3.7; Standard care: -1.2 Between group: p=0.002
							SF-36 health survey – mental component [BL to Wk 2.5]	NS
Cramer, et al. (2012) [Germany, EURO] [12]	Randomized controlled trial	Neck pain (chronic)	Thermotherapy self-treatment: mud heat pad	14 days: 20 min, once per day	Wait list	50 (25/25)	Visual Analogue Scale [BL to Dy 14]	**Reduced pain** Thermotherapy: -23.24 Waitlist: +0.04 Between group: -16.0 (p=0.003)
							Neck Disability Index [BL to Dy 14]	NS
							Short form-36 [BL to Dy 14]	NS
							Mechanical detection threshold [BL to Dy 14]	**Reduced threshold to mechanical detection** Thermotherapy: -0.22 Waitlist: +0.14 Between group: -0.35 (p=0.001)
							Vibration detection threshold [BL to Dy 14]	**Reduced threshold to vibration detection** Thermotherapy: +0.58 Waitlist: +0.01 Between group: +0.49 (p=0.032)
							Pressure pain threshold [BL to Dy 14]	NS
							Pain diary [BL to Dy 14]	**Reduced pain** Between group: F (13,585) =3.02 (p=0.013)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Cramer, et al. (2013) [Germany, EURO] [13]	Randomized controlled trial	Chronic non-specific neck pain	Iyengar yoga	9 weeks: weekly 90 minute class	Home-based exercise program (10mins daily)	51 (25/26)	Pain intensity (Visual Analogue Scale 100mm) [BL to Wk 9]	**Reduced pain intensity** Yoga -28.6; exercise -3.1 Between group 13.9 (p=0.030) Pain at motion NS
							Neck Disability Index [BL to Wk 9]	**Reduced disability** Yoga -10; exercise -0.4 Between group -7.8 (p=0.006)
							Health related quality of Life Short form-36 [BL to Wk 9]	**Improved** Between groups: Bodily pain (7.8, p=0.001) Social functioning (6.0, p=0.027) Emotional role functioning (7.9, p=0.005) Mental quality of life (6.1, p=0.016)
							Range of Motion [BL to Wk 9]	**Increased ROM** Yoga 32.5; exercise -1.0 Between group 27.1 (p=0.036)
							Joint position errors (JPE) [BL to Wk 9]	**Reduced** Yoga -2; exercise -21.1 Between group -1.8 (p=0.006)
							Pressure pain threshold [BL to Wk 9]	**Increased pressure pain threshold** At all measurement sites (Between group, p<0.05)
Cramer, et al. (2013) [Germany, EURO] [14]	12 month follow-up					36 (22/14)	Visual Analogue Scale (intensity) [BL to Mth 12]	**Reduced pain intensity** Mth 12: -16.5 (p<0.001)
							Neck Disability Index [BL to Mth 12]	**Reduced disability** Mth 12: -5.77 (p=0.001)
							Generic disability (days non-functioning) [BL to Mth 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Cramer, et al. (2013) [Germany, EURO] [15]	Secondary sub-analysis					18	Short Form-36 (SF-36) health survey [BL to Mth 12]	**Increased bodily function** Pain-related bodily function: +9.98 (p=0.005) Physical functioning: NS Physical role: NS General health: NS Vitality: NS Social functioning: NS Emotional role: NS Mental health: NS: Total physical component: NS Total mental component: NS
							Participant drawings and semi-structured interview – Physical dimension [Wk 9]	**Improved physical dimension** Renewed awareness of and approach to bodily functions. More balanced and natural perception of body.
							Participant drawings and semi-structured interview – Cognitive dimension [Wk 9]	**Improved cognitive dimension** Greater perceived control over body, health and general well-being in daily life. Feeling less controlled by pain.
							Participant drawings and semi-structured interview – Emotional dimension [Wk 9]	**Improved emotional dimension** Deep relaxation, less irritability and different perceptions of emotions. Improved coping and pain acceptance.
							Participant drawings and semi-structured interview – Behavioral dimension [Wk 9]	**Improved behavioral dimension** Use of yoga as self-help/coping strategy to relieve or prevent stress and pain. Reduced reliance on pain medication.

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Participant drawings and semi-structured interview – Social dimension [Wk 9]	**Improved social dimension** Re-engagement with preferred social activities, greater self-determination. Enriched work and social lives.
Coulson, et al. (2012) [Australia, WPRO] [29]	Uncontrolled trial	Osteoarthritis (knee)	*Perna canaliculus* (green-lipped mussel) extract	12 weeks, 15g BID	Nil	21	Lesquesne Index [BL to Wk 4 and 8]	**Reduced osteoarthritis severity** Wk 4 (-2.86, p=0.001) Wk 8 (-4.03, p<0.001)
							Western Ontario McMaster Universities Arthritis Index [BL Wk 4 and 8]	**Reduced total symptoms** Wk 4 (-11.63, p=0.001) Wk 8 (-18,833, p<0.001)
							Gastrointestinal symptom rating score [BL Wk 4 and 8]	**Reduced gastrointestinal symptoms** Wk 4 (-4.26 (p=0.004) Wk 8 (-3.96 (p=0.005)
							Rescue medication use [BL Wk 4 and 8]	14/21 used rescued medication
							Adverse symptoms [BL Wk 4 and 8]	Reflux (n=1), abdominal pain, reflux, and diarrhea (n=1), gout (n=2)
							Blood pressure [BL Wk 4 and 8]	NS
Coulson, et al. (2013) [Australia, WPRO] [30]	Randomized controlled trial	Osteoarthritis (knee)	*Perna canaliculus* (green-lipped mussel) extract	12 weeks, 15g BID	Glucosamine sulfate 1.5 g twice daily	38 (21/17)	Total fecal bacteria count, as well as levels of four genera of aerobic and six anaerobic bacteria as well as yeast [BL to Wk 12]	NS
							Lesquesne Index [BL to Wk 12]	NS
							Western Ontario McMaster Universities Arthritis Index [BL to Wk 12]	NS
							Gastrointestinal symptom rating score [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Adverse effects	NS
Haller, et al. (2016) [Germany, EURO] [16]	Randomized controlled trial	Neck pain (chronic)	Craniosacral therapy	8 weeks: craniosacral therapy, lasting 45 minutes, once per week	Sham: light touch applied to standardized anatomic areas for 2 minutes each time, once per week	54 (27/27)	Pain on Movement Questionnaire [BL, Wk 8, Wk 20]	**Reduced pain** Wk 8: CST -28.8; Sham -11.2 Between group -18.6 (p=0.001) Wk 20: CST -31.2; Sham -21.1 Between group -11.4 (p=0.020)
							Visual Analogue Scale, intensity [BL, Wk 8, Wk 20]	**Reduced pain intensity** Wk 8: CST -32.4; Sham -16.6 Between group -21.0 (p=0.001) Wk 20: CST -32.5; Sham -21.1 Between group -16.8 (p=0.003)
							Pressure pain sensitivity test [BL, Wk 8, Wk 20]	Point of max. pain: NS M. levator scapulae: NS M. trapezius: NS M. semispinalis capitis: NS
							Neck Disability Index [BL, Wk 8, Wk 20]	**Reduced disability** Wk 8: CST -14.8; Sham -4.5 Between group -8.2 (p=0.010) Wk 12: CST -13.9; Sham -5.4 Between group, -6.5 (p=0.006)
							Short Form-12, Physical [BL, Wk 8, Wk 20]	**Increased quality of life** Physical Wk 8: CST +9.2; Sham +2.1 Between group -8. (p=0.010) Wk 12: CST +10.5; Sham +2.0 Between group -6.5 (p=0.006)
							Short Form-12, Mental [BL, Wk 8, Wk 20]	NS
							Questionnaire for Assessing Subjective Physical Wellbeing [BL, Wk 8, Wk 20]	NS
							Hospital Anxiety and Depression Scale [BL, Wk 8, Wk 20]	**Reduced Anxiety** Wk 8: CST -1.6; Sham -0.1 Between group -1.0 (NS) Wk 20: CST -1.9; Sham +0.7 Between group -2.1 (p=0.020) Depression: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Perceived Stress Questionnaire [BL, Wk 8, Wk 20]	NS
							Emotional/Rational Disease Acceptance Questionnaire [BL, Wk 8, Wk 20]	NS
							Scale of Body Connection [BL, Wk 8, Wk 20]	NS
							Global Impression of Improvement [BL, Wk 8, Wk 20]	**Increased impression of improvement** Wk 8: CST 2.2; Sham 3.3 Between group -1.0 ($p<0.001$) Wk 20: CST 2.3; Sham 3.1 Between group -0.7 ($p=0.029$)
Hohmann, et al. (2012) [Germany, EURO] [17]	Randomized controlled trial	Chronic neck pain (CNP) / low back pain (LBP)	Home-based, self-administered needle stimulation pad: press both hands (CNP group) or both feet (LBP group) on the pad, then place the pad on a soft base (e.g., bed) and lie on top of the mat with the neck (CNP group) or back (LBP group) uncovered. Pain medication with the exception of corticosteroids, physiotherapy	14 days: 10 minutes per day for hands or feet; 30 minutes for neck or back.	Waitlist	82	Pain, Numeric Rating Scale [BL to Dy 14]	**Reduced pain** CNP: -1.6 ($p=0.021$) LBP: -2.3 ($p<.001$)
							Mechanical Detection Threshold [BL to Dy 14]	NS
							Vibration Detection Threshold [BL to Dy 14]	NS
							Pressure Pain Threshold (area of maximum pain) [BL to Dy 14]	**Increased threshold to pain** CNP: +0.106 ($p = .032$) LBP: +0.082 ($p = .013$)
							Pressure Pain Threshold (10cm close to area of maximum pain) [BL to Dy 14]	**Increased threshold to pain** CNP: NS LBP: +0.073 ($p = .018$)
							Neck Pain Questionnaire [BL to Dy 14]	**Reduced neck pain** CNP: -7.4 ($p = 0.028$)
							Oswestry Disease Index [BL to Dy 14]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Lauche, et al. (2011) [Germany, EURO] [18]	Randomized controlled trial	Chronic non-specific neck pain	Dry cupping therapy: performed according to patient pain diagram and physical examination to determine areas of muscle tension and myogeloses	10-20 min, every 3-4 days for five treatments	Waitlist	50 (25/25)	Pain at rest, Visual Analog Scale [BL to Day 18]	**Reduced pain at rest** Cupping: -19.4; Waitlist: +4.8 Between groups – 22.5 (p=0.00002)
							Maximal pain related to movement, Visual Analog Scale [BL to Dy 18]	**Reduced movement-related pain** Cupping: -33; Waitlist: -12.9 Between groups -17.8 (p=0.01)
							NDI [BL to Dy 18]	**Reduced neck disability** Cupping: -6.4; Waitlist: +0.1 Between groups -6.3 (p=0.002)
							Short Form-36 [BL to Dy 18]	**Increased Quality of Life** Bodily pain Cupping: +13.4; Waitlist: -2.9 Between groups 13.8 (p=0.006) Vitality Cupping: +8.9; Waitlist: +0.5 Between groups 10.2 (p=0.006) Social function Cupping: +11.9; Waitlist: -1.1 Between groups 5 (p=0.06) Mental Health Cupping: +5; Waitlist: -4.7 Between groups 11.4 (p=0.04) Physical functioning: NS Role physical: NS General health perception: NS Role emotional: NS Mental health: NS Physical Component Score: NS
							MDT at two pain-related and control areas [BL to Dy 18]	NS
							PPT at two pain-related and control areas [BL to Dy 18]	**Pain thresholds increased in cupping, decreased in waitlist** pain-related areas

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Cupping: -0.5; Waitlist: -0.4 Between groups 0.08 (p=0.026) pain-adjacent areas Cupping: +0.4; Waitlist: -0.7 Between groups 11 (p=0.001) Hand Cupping: +0.1; Waitlist: -0.8 Between groups 0.07 (p=0.034) Foot Cupping: +0.19; Waitlist: +0.06 Between groups 0.12 (p=0.004)
							VDT at two pain-related and control areas [BL to Dy 18]	NS
Lauche, et al. (2012) [Germany, EURO] [19]	Randomized controlled trial	Chronic, non-specific neck pain	Cupping therapy: superficial incisions made at areas of pain, and covered with double-walled glass cups using flame-generated vacuum	15 minutes (+ 3 day washout): 1 cupping treatment; 10-15 minutes	Waitlist control	50 (25/25)	Pain at rest, Visual Analog Scale [BL to 15 minutes]	**Reduced pain at rest** Cupping: -16.4; Waitlist: +3.1 Between group: -17.9 pts (p=0.003)
							Maximal pain related to movement, Visual Analog Scale [BL to Dy 3]	**Reduced movement-related pain** Cupping: -24.8; Waitlist: -11.8 Between group: -19.7 pts (p = 0.003)
							Neck Disability Index [BL to Dy 3]	NS
							Short Form-36 [BL to Dy 3]	**Increased Quality of Life** Physical functioning: Cupping, +5.5; Waitlist, -1.1 Between group, +7.5 (p = 0.017) Bodily pain: Cupping, +15.3; Waitlist, -0.4 Between group, +14.9 (p = 0.007) Physical component score: Cupping, +5.5; Waitlist, +1.1 Between group, +5.0 (p = 0.008)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Role physical: NS General health perception: NS Vitality: NS Social function: NS Role emotional: NS Mental health: NS Mental Component Score: NS
Lauche, et al. (2013) [Germany, EURO] [20]	Secondary analysis of 4 trials	Chronic non-specific neck pain	Wet cupping treatment (single application), Dry cupping (5 applications), Pulsating cupping (5 applications), of Cupping massage (5 applications) (2 yr follow-up post-intervention, pooled across four studies)	2 years Follow-up post intervention	Nil	133	Pain intensity, Visual Analog Scale [BL to Mth 24]	NS
							Functional Disability (NDI) [BL to Mth 24]	**Reduced disability** -3.5 (p=0.025)
							SF-36 [BL to Mth 24]	**Increased quality of life** Bodily pain +14.6 (p<0.001) Physical component study +3.0 (p=0.004)
Lauche, et al. (2013) [Germany, EURO] [21]	Randomized controlled trial	Chronic neck pain	Self-directed partner-delivered cupping massage	12 weeks: 10-15 min, twice per wk, for 12 wks, with initial 1 hr workshop training	Progressive muscle relaxation	61 (30/31)	Pain intensity, Visual Analog Scale [BL to Wk 12]	NS
							Pain on motion, Visual Analog Scale [BL to Wk 12]	NS
							Pain Description List [BL to Wk 12]	NS
							Neck Disability Index [BL to Wk 12]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 12]	NS
							Short Form-36 [BL to Wk 12]	NS
Lauche, et al. (2016) [Germany, EURO] [31]	Randomized controlled trial	Osteoarthritis (knee)	Cabbage leaf wraps (CLW) (1-2 leaves applied as a poultice)	4 weeks: 2hrs per day	Diclofenac gel (TPG) and usual care (UC)	81 (27/27/27)	Pain intensity, Visual Analog Scale [BL to Wk 4, Wk 12]	**Reduced pain** UC Wk 4: Between group -12.2 pts (p=0.033) Wk 12: NS TPG Wk 4: NS Wk 12: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Western Ontario and McMaster Universities Arthritis Index [BL to Wk 4, Wk 12]	**Reduced disability** Pain Wk 4: Cabbage leaf -1.3; Usual care +0.2 Between group (UC) -1.3 (p=0.002) Between group (TPG) NS Wk 12: Cabbage leaf -1.0; Usual care +0.2 Between group (UC) -1.1 (p=0.009) Between group (TPG) NS Stiffness Wk 4: Cabbage leaf -1.0; Usual care +0.3 Between group (UC) -1.1 (p=0.031) Between group (TPG) NS Wk 12: Cabbage leaf -1.0; Usual care +0.4 Between group (UC) -1.1 (p=0.039) Between group (TPG) NS Physical function Wk 4: Cabbage leaf -0.9; Usual care +0.3 Between group (UC) -1.2 (p=0.002) Between group (TPG) NS Wk 12: Cabbage leaf -0.8; Usual care +0.3 Between group (UC) -1.0 (p=0.017) Between group (TPG) NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Short Form-36 [BL to Wk 4, Wk 12]	**Increased Quality of Life** Physical component Wk 4: Cabbage leaf +4.1; Usual care +1.3; Diclofenac -0.9 Between group (UC) NS Between group (TPG) +5.0 (p=0.004) Wk 12: Cabbage leaf +4.5; Usual care +0.1; Diclofenac -2.2 Between group (UC) +4.3 (p=0.007) Between group (TPG) +7.8 (p=0.0001) Physical functioning Wk 4: Cabbage leaf +7.2; Usual care -2.5 Between group (UC) +9.4 (p=0.004) Between group (TPG) NS Wk 12: Cabbage leaf +8.3; Usual care -0.9; Diclofenac -0.9 Between group (UC) +9.0 (p=0.019) Between group (TPG) +12.0 (p=0.026) Physical role functioning Wk 4: NS Wk 12: Cabbage leaf +5.5; Diclofenac -16.4 Between group (UC) NS Between group (TPG) +22.1 (p=0.024)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Bodily pain Wk 4: NS Wk 12: Cabbage leaf +9.0; Usual care -1.2; Diclofenac -1.7 Between group (UC) +10.7 (p=0.007) Between group (TPG) +13.7 (p=0.003) General health perception Wk 4: NS Wk 12: Cabbage leaf +3.7; Diclofenac -5.0 Between group (UC) NS Between group (TPG) +8.9 (p=0.024) Mental component: NS Vitality: NS Social role functioning: NS Emotional role functioning: NS Mental health: NS
							Arthritis-specific self-efficacy short-form scale [BL to Wk 4, Wk 12]	NS
							Physical Function (30 second Chair Stand Test) [BL to Wk 4]	**Reduced Pain** Number of sit ups: NS Pain: Cabbage leaf -1.2 Usual care -0.4 Between group (UC) -1.4 (p=0.003) Diclofenac -0.1 Between group (TPG) -1.3 (p=0.033)
							Pressure Pain Sensitivity Threshold [BL to Wk 4]	**Increased threshold to pressure pain** Maximum: NS Quadriceps muscle: Cabbage leaf, +16.5;

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Usual care -64.1; Diclofenac -53.2 Between group (UC) +77.8 (p=0.010) Between group (TPG) +90.2 (p=0.039) Pes anserinus: Cabbage leaf +59.1; Usual care -31.3 Between group (UC) +127.1 (p=0.010) Between group (TPG) NS Lateral joint line: NS
Lauche, et al. (2016) [Germany, EURO] [22]	Randomized controlled trial	Chronic non-specific neck pain	Group 1: Tai chi (Yang style): 5-10 minute warm up, Tai Chi form practice, and 5-10 minute relaxation; asked to practice 15 minutes per day outside of class Group 2: Neck exercises: rehabilitation exercises including education for a healthy back; ergonomic principles, proprioceptive exercises, isometric and dynamic stabilization, stretching, and strengthening neck and core exercises; 5-10 minute warm up and relaxation exercises at end; asked to execute exercises 15 minutes per day	12 weeks: Tai chi -75-90 min/wk Neck exercises 60-75 min/wk session	Waitlist	114 (38/37/39)	Visual Analogue Scale, intensity [BL to Wk 12]	**Reduced pain intensity** Tai chi: -18.0; Waitlist: -9.7 Between group (WL): -10.5 (p=0.033) Between group (Neck): NS
							Pain on Movement [BL to Wk 12]	**Reduced pain on movement** Tai chi: -14.9; Waitlist: -2.2 Between group (WL): -12.0 (95% CI -18.7 to -5.4) Between group (Neck): NS
							Neck Disability index [BL to Wk 12]	**Reduced neck disability** Tai chi: -9.3; Waitlist: -1.8 Between group (WL): -7.2 (95% CI -11.7 to -2.7) Between group (Neck): NS
							Disability in days [BL to Wk 12]	NS
							Everyday function, Visual Analogue Scale [BL to Wk 12]	**Reduced impact on everyday function** Tai chi: -12.8; Waitlist: -2.3 Between group (WL): -9.9 (95% CI -17.8 to -2.1) Between group (Neck): NS
							Leisure, Visual Analogue Scale [BL to Wk 12]	**Reduced impact on leisure** Tai chi: -16.9; Waitlist: -7.4 Between group (WL): -9.9 (95% CI -19.0 to -0.7) Between group (Neck): NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Short Form-36 [BL to Wk 12]	**Increased quality of life** Physical component Tai chi, +3.17; Waitlist, -0.7 Between group (WL), +4.1 (95% CI +1.1 to +7.0) Between group (Neck), NS Physical functioning Tai chi, +2.6; Waitlist, -4.5 Between group (WL), +7.0 (95% CI +0.1 to +13.9) Between group (Neck), NS Bodily pain: Tai chi, +12.2; Waitlist: -0.3 Between group (WL): +9.1 (95% CI +2.1 to +16.0) Between group (Neck): NS Vitality: Tai chi, +5.1; Waitlist: -0.2 Between group (WL): +5.5 (95% CI +0.5 to +10.5) Between group (Neck): NS Mental component: NS Physical role functioning: NS General health perception: NS Social role functioning: NS Emotional role functioning: NS Mental health: NS
							Hamilton Anxiety and Depression Score [BL to Wk 12]	NS
							General wellbeing [BL to Wk 12]	**Increased wellbeing** Ability to enjoy: Tai chi, +0.6; Waitlist: -0.6 Between group (WL): +1.1 (95% CI +0.1 to +2.0) Between group (Neck): NS Resilience: NS Vitality: NS Ease of mind: NS
							Perceived Stress Scale [BL to Wk 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Multidimensional Assessment of Interoceptive awareness [BL to Wk 12]	**Increased interoceptive awareness** Trusting: Tai chi, +0.3; Waitlist: +0.0 Between group (WL): +0.3 (95% CI +0.0 to +0.6) Between group (Neck): NS Noticing: NS Not distracting: NS Not worrying: NS Attention regulation: NS Emotional awareness: NS Self-regulation: NS Body listening: NS
Lauche, et al. (2016) [Germany, EURO] [36]	Randomized controlled trial	Fibromyalgia Syndrome	Cupping therapy on upper and lower back	18 days: 30 min, 5 sessions	Sham cupping control, Usual care (as waitlist control)	141 (47/48/46)	Pain Visual Analog Scale [BL to Dy 18]	**Reduced pain** Between group (UC), -12.4 ($p<0.001$) Between group (Sham), NS
							Fibromyalgia Impact Questionnaire [BL to Dy 18]	NS
							Short Form-36 [BL to Dy 18]	**Increased quality of life** Bodily pain: Cupping, +9.4; Usual care, +7.0 Between group (UC), +4.7 Between group (Sham), NS Mental component: Cupping, +2.8; Usual care, +0.2 Between group (UC), +3.4 (95%CI 0.8-5.9) Between group (Sham), NS Vitality: Cupping, +5.4; Usual care, -0.6 Between group (UC), +6.3 (95%CI 0.9-11.7) Between group (Sham), NS Social role functioning: Cupping, +5.3; Usual care, -1.1 Between group (UC), +7.1 (95%CI 0.1-14.1) Between group (Sham), NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Mental health: Cupping, +4.2; Usual care, 10.2 Between group (UC), +4.5 (95%CI 0.0-8.9) Between group (Sham), NS Physical component: NS Physical functioning: NS Physical role functioning: NS General health perception: NS Emotional role functioning: NS
							Pain perception [BL to Dy 18]	NS
							Fatigue [BL to Dy 18]	**Reduced motivation** Reduced motivation: Cupping, -0.2; Usual care, -0.4 Between group (UC), -1.2 Between group (Sham), NS General fatigue: NS Physical fatigue: NS Reduced activity: NS Mental fatigue: NS
							Sleep [BL to Dy 18]	NS
							Pressure pain sensitivity [BL to Dy 18]	NS
Myers, et al. (2010) [Australia, WPRO] [32]	Randomized controlled trial	Osteoarthritis (knee)	Maritech seaweed extract	12 weeks: 1000 mg/day	100 mg/day	12 (5/7)	Comprehensive Arthritis Test (COAT) score [BL to Wk 12]	**Reduced arthritis symptoms** Average: 100mg, -0.91; 1000mg, -3.05 Between group, p=0.043 Physical difficulties 100mg, -0.138; 1000mg, -2.402 Between group, p=0.010 Overall: 100mg, -0.848; 1000mg, -2.455 Between group, p=0.044 Pain: NS Stiffness: NS
							Adverse events	No adverse events were due to the treatment

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Myers, et al. (2016) [Australia, WPRO] [34]	Randomized controlled trial	Osteoarthritis (hip and knee)	*Fucus vesiculosus* extract (85% fucoidan)	12 weeks: 300 mg/day	Placebo	96 (54/42)	Comprehensive Arthritis Test (COAT) score [BL to Wk 12]	NS
							Paracetamol Use [BL to Wk 12]	NS
							Body mass index (kg/m^2) [BL to Wk 12]	NS
							Adverse events	NS
Nandini, et al. (2018) [India, SEARO] [23]	Randomized controlled trial	Non-specific or common neck pain	Hot sand fomentation with yoga (stretching, *asanas*, *pranayama*, relaxation and meditation techniques, lecture on yoga philosophy), low fat and low salt vegetarian diet, and sesame seed oil topical application	5 days: 15 min/day	Yoga, dietary changes and sesame seed oil application only	60 (30/30)	Visual Analog Scale [BL to Dy 5]	**Reduced pain** Hot Sand: -5.18; Control: -1.54 Between group: p<0.001
							Neck Disability Index [BL to Dy 5]	**Reduced neck disability** Hot Sand: -23.27; Control: -11.07 Between group: p<0.001
							Pittsburg Sleep Quality Index [BL to Dy 5]	NS
							Short Form-36 health survey, version 2 [BL to Dy 5]	**Increased quality of life** Social Functioning Hot Sand: +26.5; Control: +15.25 Between group: p=0.035 Pain Hot Sand: +28.25; Control: +10.09 Between group: p<0.001 Physical functioning: NS Physical health: NS Emotional problem: NS Energy: NS Emotional wellbeing; NS General Health: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Perlman, et al. (2012) [USA, AMRO] [33]	Randomized controlled trial	Osteoarthritis (knee)	Swedish Massage Therapy	8 weeks: Group 1: 30 min massage/week Group 2: 4 weeks of 30 min massage twice a week + 4 weeks of 30 min massage once per week Group 3: 60 min massage/week Group 4: 4 weeks of 60 min massage twice a week + 4 weeks of 60 min massage once per week	Usual care (no massage)	125 (25/25/ 25/25/ 25)	Western Ontario and McMaster Universities Arthritis Index [BL to Wk 8]	**Reduced arthritis symptoms** Pain: Group 1, NS; Group 2, NS; Group 3, -27.2 Group 4, -27.7; Usual care, -5.6 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Functionality Group 1, NS; Group 2, NS; Group 3, -21.2; Group 4, -22.0; Usual care, -6.6 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Global Group 1, NS; Group 2, NS; Group 3, -24.0; Group 4, -24.0; Usual care, -6.3 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05 Stiffness: NS
							Visual Analog Scale [BL to Wk 8]	**Reduced pain** Group 1, NS; Group 2, NS; Group 3, -39.8; Group 4, -31.2; Usual care, -9.8 Between group (1&2 vs UC), NS Between group (3&4 vs UC), p<0.05
							Flexion Range of Motion [BL to Wk 8]	NS
							Measured time to walk 50 feet [BL to Wk 8]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Pullan, et al. (2016) [India, SEARO] [24]	Randomized controlled trial	Chronic neck pain	Acupuncture (acu) (SI 1,3,6,14,15,GB-20,21,SJ-15,UB-10 naturopathy (hydrotherapy, bodywork, diet, yoga)	10 days	Moist heat (local application of heat or cold) and naturo- pathy (hydrotherapy, bodywork, diet, yoga)	60 (30/30)	Visual Analogue Scale [BL to Dy 10]	NS
							Neck Disability Index [BL to Dy 10]	NS
							State Trait Anxiety Inventory [BL to Dy 10]	**Reduced anxiety in hydrotherapy group** (2.20 – 1.83, p=0.02)
							Short Form-36 (SF-36) health survey – Physical functioning [BL to Dy 10]	NS
							SF-36 – limitations, physical health [BL to Dy 10]	NS
							SF-36 – limitations, emotional problems [BL to Dy 10]	**Reduced emotional problems** Between group: p=0.01
							SF-36 – emotional wellbeing [BL to Dy 10]	NS
							SF-36 – social functioning [BL to Dy 10]	NS
							SF-36 – energy/fatigue [BL to Dy 10]	NS
							SF-36 health survey – bodily pain [BL to Dy 10]	NS
							SF-36 – general health [BL to Dy 10]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Ritenbaugh, et al. (2008) [USA, AMRO] [38]	Randomized controlled trial	Temporomandibular disorder	Group 1: Traditional Chinese medicine (TCM) including acupuncture, herbal therapy, massage, relaxation tapes, 2 visits per week for 6 wks, then 1 per week for 5-6 mths. Group 2: Naturopathic medicine (NM) including herbal medicine, nutritional supplements, nutritional and lifestyle advice, stress-reduction advice,	6-8 mths (+ 3 mths follow up)	Speciality dental care for TMD treatment including education, bite splints, self-care counselling and pain management strategies, 2 hr class sessions plus optional referrals for massage, psychologic and counselling support. (9.5 hours)	128 (42/36/ 50)	Worst Facial Pain [BL to Mth 6/8, 9/11]	**Reduced worst facial pain** Mth 6/8: TCM, -2.2; NM: -2.3; Specialty: -1.2 Between group (Specialty vs TCM): p=0.010 Between group (Specialty vs NM): p=0.025 Mth 9/11: TCM, -2.5; NM: -3.2; Specialty: -1.7 Between group (Specialty vs TCM): p=0.037 Between group (Specialty vs NM): p=0.019
							Average Facial Pain [BL to Mth 6/8, 9/11]	**Reduced average facial pain** Mth 6/8: TCM, -1.9; NM: NS; Specialty: -0.9 Between group (Specialty vs TCM): p=0.004 Between group (Specialty vs NM): NS Mth 9/11: TCM, -2.3; NM: NS; Specialty: -1.5 Between group (Specialty vs TCM): p=0.017 Between group (Specialty vs NM): p=NS
							Impact on Social Life [BL to Mth 6/8, 9/11]	Mth 6/8: TCM, NS; NM: -1.2; Specialty: -0.5 Between group (Specialty vs TCM): NS Between group (Specialty vs NM): p=0.012 Mth 9/11: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Saha, et al. (2019) [Germany, EURO] [39]	Randomized controlled trial	Migraine and/or tension-type headache comorbid with temporomandibular disorder (TMD).	Occlusal splint therapy (plus usual care)	12 weeks	Usual care	60 (30/30)	Headache intensity (Visual Analogue Scale 0-100mm) [Wk 1 to Wk 12 and 24 (only intervention)]	**Reduced intensity** Wk 12 Occlusal splint -3.6 ($p<0.001$) vs +6.6 Between group: NS Wk 24 Occlusal splint -10.3 ($p<0.001$)
							Headache days (headache diary) [Wk 1 to Wk 12 and 24 (only intervention)]	NS
							Headache hours (headache diary) [Wk 1 to Wk 12 and 24 (only intervention)]	NS
							Short Form-36 [Wk 1 to Wk 12 and 24 (only intervention)]	**Increased physical quality of life** Wk 12 Occlusal splint 4.1 $p<0.001$) vs -0.6 (NS) Between group: NS Wk 24 Occlusal splint 4.1 ($p<0.001$)
Saha, et al. (2016) [Germany, EURO] [27]	Uncontrolled trial	Low back pain (chronic)	Mechanical needle stimulation pad	14 weeks: 45 minutes needle pad use per day	Nil	91	Visual Analogue Scale [BL to Wk 2, Wk 14]	NS
							Oswestry Disability Index [BL to Wk 2, Wk 14]	**Reduced disability** Wk 2: -4.6 ($p<0.001$) Wk 14: -4.3 ($p<0.001$)
							Short Form-36 [BL to Wk 2, Wk 14]	**Increased quality of life** Physical component: Wk 2, +3.8 ($p<0.001$); Wk 14, +2.5 ($p=0.008$) Physical functioning: Wk 2, +6.4 ($p=0.001$); Wk 14, +5.6 ($p=0.002$) Vitality: Wk 2: +3.3 ($p=0.045$); Wk 14: NS Mental component: NS Physical role functioning: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Bodily pain: NS General health perception: NS Social role functioning: NS Emotional role functioning: NS Mental health: NS
							Fear avoidance behavior [BL to Wk 2, Wk 14]	NS
							Days under medication per week [BL to Wk 2, Wk 14]	**Reduced days under medication per week** Wk 2: -1.2 (p=0.015) Wk 14: NS
Saha, et al. (2017) [Germany, EURO] [25]	Randomized controlled trial	Chronic non-specific neck pain	Cupping Massage	3 weeks: twice per week for a total of 5 treatments	Waitlist	50 (25/25)	Pain on Movement Questionnaire [BL to Wk 3]	**Reduced pain on movement** Cupping: -10.4; Waitlist: -2.7 Between group: -11.7 (p=0.019)
							Visual Analogue Scale, intensity [BL to Wk 3]	**Reduced pain intensity** Cupping: -29.9; Waitlist: -2.3 Between group: -14.3 (p=0.037)
							Neck Disability Index [BL to Wk 3]	**Reduced neck disability** Cupping: -3.6; Waitlist: -0.3 Between group: -4.1 (p < 0.0001)
							Short Form-36 [BL to Wk 3]	**Increased quality of life** Bodily pain: Cupping, +15.6; Waitlist, +0.5 Between group, +16.7 points (p = 0.002) Mental health: Cupping, +7.7; Waitlist, -0.5 Between group, +8.5 (p = 0.003) Mental component: Cupping, +4.3; Waitlist, +0.4 Between group, +4.3 (p = 0.036) Physical component: NS Physical functioning: NS Physical role functioning: NS General health perception: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Vitality: NS Social role functioning: NS Emotional role functioning: NS
							Pressure-pain threshold [BL to Wk 3]	**Increased threshold to pressure pain** Between group: improvement at site of maximal pain (p=0.022)
							Mechanical detection threshold [BL to Wk 3]	NS
							Vibration detection threshold [BL to Wk 3]	NS
							2-point discrimination threshold [BL to Wk 3]	NS
Saha, et al. (2019) [Germany, EURO] [26]	Randomized controlled trial	Low back pain (chronic non-specific)	*Gua Sha* Therapy	Two treatments 7 days apart (Dy 1 and Dy 7)	Waitlist control	50 (25/25)	Pain on Movement Questionnaire [BL to Day 12]	**Reduced pain on movement** Gua Sha: -24.55 Waitlist: -12.3 Between group: ($p < 0.001$)
							Oswestry Low Back Pain Disability Questionnaire [BL to Day 12]	NS
							Pressure-pain threshold [BL to Day 12]	NS
							Mechanical detection threshold [BL to Day 12]	NS
							Vibration detection threshold [BL to Day 12]	NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
Saper, et al. (2017) [USA, AMRO] [28]	Randomized controlled trial	Low back pain (chronic non-specific)	Yoga class (relaxation exercises, *pranayama*, discussion of yoga philosophy, *asanas*) supplemented with at-home daily practice materials. Following initial program, participants are re-randomized to a structured yoga maintenance program or no structured maintenance. OR Physical therapy class (specific exercises, or stabilization exercises) supplemented with at-home daily exercises. Following initial program, participants are re-randomized to a structured physical therapy maintenance program or no structured maintenance.	64 weeks: Yoga – (Week 1-12) 75-minute class per week; (Week 13-52) Structured maintenance or no structured maintenance Physical therapy – (Week 1-12) 60 minute class per week; (Week 13-52) Structured maintenance or no structured maintenance	Educational pamphlet – 'The Back Pain Helpbook" with assignment sheet	320 (127/129/64) Yoga – structured: 64/ not structured: 64 PT – structured: 64/ not structured: 64	Modified Roland Morris Disability Questionnaire [BL to Wk 12]	**Reduced disability** ⩾30% reduction in Score: Yoga v PT, NS Yoga v Education, 3.1 (95% CI 1.6 to 6.2) PT v Education, 2.0 (95% CI 1.0 to 4.0) ⩾30% reduction in back pain: Yoga v PT, NS Yoga v Education, NS PT v Education, 2.3 (95% CI 1.1 to 4.5)
							Back pain intensity score [BL to Wk 12]	**Reduced back pain** Yoga: -1.7; PT: -2.3; Education: -1.4 Between group (PT v Education): -0.84 (95% CI -1.5, -0.18) Between group (Yoga v PT): NS Between group (Yoga v Education): NS
							Self-reported Pain Scale [BL to Wk 12]	**Reduced pain** After 12 weeks, improvement in pain score for yoga intervention was non-inferior to that seen in control PT group (-1.7 and -2.3, respectively)
							Self-reported pain medication use in the past week [BL to Wk 12]	**Reduced medication use** Any pain medication: Yoga v PT, NS; Yoga v Education, 0.36 (95% CI 0.17 to 0.78); PT v Education, 0.31 (95% CI 0.14 to 0.67) Acetaminophen: Yoga v PT, 1.9 (95% CI 1.0 to 3.7); Yoga v Education, NS; PT v Education, 0.45 (95% CI 0.21 to 0.97) NSAIDs: NS Opioids: NS

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Global improvements [BL to Wk 12]	NS
							Patient satisfaction with intervention [BL to Wk 12]	**Increased patient satisfaction** Yoga v PT, NS; Yoga v Education, 2.8 (95% CI 1.4 to 5.7); PT v Education, 3.6 (95% CI 1.8 to 7.4)
							Short Form-36 [BL to Wk 12]	NS
Szczurko, et al. (2007) [Canada, AMRO] [7]	Randomized controlled trial	Low back pain (chronic non-specific)	Naturopathic care consisting of acupuncture, breathing exercises, nutritional counseling and physical exercises	12 weeks: twice per week	Standardized educational booklet on exercise and relaxation exercises	75 (39/36)	Oswestry Low Back Pain Disability Questionnaire [BL to Wk 12]	**Reduced low back pain** NM: -5.0; Education: -0.0 Between group: p<0.0001
							Short Form-36 [BL to Wk 12]	**Increased quality of life** Physical component: NM, +9.25; Education, +0.78 Between group, +8.47 (p<0.0001) Mental component: NM, +4.26; Education, -2.74 Between group, +5.56 (p<0.0045) Physical functioning: NM, +7.12; Education, +1.56 Between group, +5.56 (p<0.0033) Physical role: NM, +8.67; Education, -2.81 Between group, +11.48 (p<0.001) Bodily pain: NM, +11.12; Education, +0.29 Between group, +10.83 (p<0.0001) General health: NM, +6.05; Education, -1.13 Between group, +7.18 (p=0.0002) Vitality: NS Social functioning. NM, +8.95; Education, -1.62

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
								Between group, +10.57 (p<0.0001) Emotional role: NM, +4.88; Education, -3.17 Between group, +8.05 (p=0.0090) Mental health: NM, +4.62; Education, -2.82 Between group, +7.44 (p=0.0003)
							Self-reported Pain Scale [BL to Wk 12]	**Reduced pain** NM: -1.0; Education: -0.0 Between group: p<0.0001
							Roland Morris Disability Questionnaire [BL to Wk 12]	**Reduced disability** NM: -4.0; Education: +2.0 Between group: p<0.0001
							Forward Lumbar Flexion Range of Motion (cm) [BL to Wk 12]	**Increased range of motion** NM: +4.5; Education: -0.5 Between group: p<0.0001
							Weight (kg) [BL to Wk 12]	**Reduced weight** NM: -1.51; Education: -0.05 Between group: p<0.0052
							Body Mass Index (kg/m^2) [BL to Wk 12]	**Reduced BMI** NM: -0.58; Education: -0.06 Between group: p<0.0106
							NSAID Use (pills per week) [BL to Wk 12]	**Reduced medication use** NM: -1.0; Education: +1.3 Between group: not reported
Szczurko, et al. (2009) [Canada, AMRO] [8]	Randomized controlled trial	Rotator cuff tendonitis	Naturopathic care: dietary counseling (increased consumption of fish, berries, fruits, vegetables, nuts and whole grains; reduced alcohol), standardized acupuncture (LI15, SJ14, SI 19, SI10-13, BL41-46), nutritional supplement (Phlogenzym – bromelain, 90mg; trypsin, 48mg; rutin, 100mg)	12 weeks: 30 minute visits per week including 10 minute acupuncture treatments; two tablets three times daily	Standardized physical exercise	85 (43/42)	Shoulder Pain and Disability Index [BL to Wk 12]	**Reduced pain and disability** Total: NM, -42.34; PE, -23.59 Between group, -29.66 (p<0.0001) Pain: NM, -18.70; PE, -5.7 Between group, -13.00 (p<0.0001) Disability: NM, -21.64; PE, -6.00 Between group, -15.64 (p=0.0002)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Pain Visual Analog Scale [BL to Wk 12]	**Reduced pain** NM: -2.34; PE: -0.67 Between group: -1.67 (p<0.0001)
							Short Form-36 [BL to Wk 12]	**Increased quality of life** Physical component; NM, +7.75; PE, +2.04 Between group, +5.71 (p=0.0004) Mental component: NM, +5.85; PE, +0.13 Between group, +5.73 (p=0.0107) Physical functioning: NM, +14.88; PE, +1.36 Between group, +13.52 (p=0.0025) Physical role: NM, +21.09; PE, +3.75 Between group, +17.34 (p=0.0015) Bodily pain: NM, +24.16; PE, +7.64 Between group, +16.52 (p=0.0004) General health: NM, +10.07; PE, -1.54 Between group, -11.62 (p=0.0029) Vitality: NM, +14.33; PE, +4.17 Between group, +10.16 (p=0.0047) Social function: NM, +14.02; PE, +3.65 Between group, +10.38 (p=0.0378) Emotional role: NM, +13.82; PE, -2.27 Between group, +16.09 (p=0.0020) Mental health: NM, +12.44; PE, -2.22 Between group, +14.66 (p=0.0015)

Author (year) [Country, World Region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or comparison group	No. participants (Intervention/ Control)	Measure of Outcome	Outcome
							Measure Yourself Medical Outcomes Profile [BL to Wk 12]	**Reduced symptoms** MYMOP Symptom 1: NM, -2.20; PE, -1.29 Between group, -0.91 (p=0.0225) MYMOP Symptom 2: NM, -3.13; PE, -0.66 Between group, -1.86 (p=0.0001)

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24 Neurological Conditions

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HIGHLIGHTS

- Neurological conditions are listed in the top 10 reasons patients seek naturopathic care.
- The main neurological conditions treated by naturopaths/NDs include headaches and migraines, neuralgia, ADD/ADHD, Parkinson's disease, memory loss, autism and disorders related to brain injuries.
- Naturopaths/NDs use a range of therapies in the treatment of neurological conditions.
- There is a growing body of research supporting the role of naturopathic care in the treatment of neurological conditions.
- 66.7% of clinical studies investigating naturopathic treatments for neurological conditions reported a positive outcome in at least one primary or secondary outcome measure.

According to the Global Burden of Disease Study, neurological conditions are the second leading cause of death after heart disease and the leading cause of disability worldwide [1]. Neurological conditions are emerging as an important treatment priority, with further substantial increases in absolute numbers of deaths and people with disabilities due to neurological diseases rising substantially as a result of population growth and ageing [2]. Neurological disorders are diseases of the central and peripheral nervous system. They can be categorized as general neurological conditions (e.g., nerve pain, attention deficit or hyperactivity disorder (ADD/ADHD), seizures, tinnitus), disorders of movement (e.g., Parkinson's Disease (PD)), neuropathies (e.g., neuralgia, optic neuropathy, peripheral neuropathy) and dementia-type disorders (e.g., memory loss, dementia, Alzheimer's Disease).

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=21) naturopathic clinicians undertook in the field of neurological research. This research includes a total of 1176 participants and was conducted in the United States of America (USA) (n=11), India (n=6), Germany (n=2), Australia (n=1) and Egypt (n=1). The study designs include randomized controlled trials (n=11), case reports (n=5), non-randomized controlled trials (n=2) and cohort studies (n=2). The studied interventions include clinical nutrition (n=7), complex naturopathic interventions (n=3), yoga (n=3), acupuncture (n=4) and one study each of herbal medicine, hydrotherapy, homeopathy, and bodywork (healing touch).

The main neurological conditions examined in these studies included adults with headaches and migraines (n=7), Parkinson Disease (n=4), attention deficit hyperactivity disorder (ADHD) (n=3), Alzheimer's disease (n=2), Traumatic Brain Injury (n=2), autism (n=2) and Transverse myelitis (n=1). Of all the naturopathic clinical studies examining neurological condition populations, 66.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 24.1: Clinical research investigating neurological conditions conducted by naturopathic researchers.* This body of naturopathic research on neurological conditions is also supported by more than 40 observational studies and 25 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Neurological conditions are listed in the top ten primary health conditions for which individuals consult with a naturopathic clinician globally [3]. The neurological conditions most often reported by patients seeking naturopathic care include headaches and migraines, neuralgia, ADD/ADHD, memory loss, PD, autism and disorders related to brain injuries. Naturopathic research has examined diverse neurologic conditions and used multiple therapies and interventions in the treatment and management of neurological disorders. Although the

research is limited, some studies show promising effects for neurological conditions that warrant further research and practice attention.

The paucity of research in this area meant that few interventions were investigated by more than one study in the same condition, and research has focused on single interventions rather than complex naturopathic whole practice. However, there is considerable breadth in the types of interventions examined by naturopathic researchers in neurological disorders, which suggests that the growing evidence-base for complementary and integrative medicine in the treatment of neurological disorders may also be relevant and transferable to naturopathic practice [4].

Neurological disorders are likely to be increasingly prevalent in clinical practice as the global population ages, with focus shifting not only to disease treatment but also preventive and health optimization approaches [5]. Such approaches to the neurological disorders align well with naturopathic approaches to treatment. The rise in absolute numbers of people affected by neurological disorders and associated disease burden suggests that advances in prevention and management of major neurological disorders are not sufficiently effective to counter global demographic changes [2]. This suggests an urgent need for innovative and integrative approaches to patient care. Emerging evidence of effectiveness and the high level of utilization of naturopathic care by the global population suggest that naturopaths/naturopathic doctors may be able to form an integral part of new innovative treatment models in neurological disorders. Given the impact of neurological conditions on global disease burden, and the high prevalence of utilization of naturopathic practitioners for neurological conditions globally, neurological conditions present a significant opportunity for future naturopathic research.

Studies based on specific conditions:

Migraine and Chronic Headaches

Seven studies, four from India [6-9], two from the USA [10, 11] and one from Germany [12] explored different naturopathic interventions for migraines and chronic headaches. A randomized controlled trial (n=60) conducted in India compared yoga exercises in a naturopathic setting, five days a week for six weeks, to usual conventional care (UC) in patients with migraines [7]. Results indicated significant improvement based on the Headache Impact Test (HIT-6) (Yoga -22.7, UC -6.8, $p<0.001$), decreased headache frequency (Yoga -9.5, UC -5.3) and intensity (Yoga -6.67, UC -1.57) and improvement in self-perceived benefit of treatment (Yoga 96.7%, UC 30%). Another randomized controlled trial conducted in India (n= 60) evaluated the impact of yoga practices such as saltwater nasal flush, water-induced self-emesis and postural and breathing exercises [6]. Of the seven scales used to measure outcomes, six showed significances in the treatment group including reduced migraine intensity (-13.0 Migraine Disability Assessment score), reduced pain (-3.2 Visual Analogue Scale (VAS)), reduced headache impact (-16.8 Headache Impact Test), and improvements on the World Health Organization Quality of Life (WHO QoL) BREF scale quality of life (+35.9), social relationships (+9.9) and environment (+4.8). A prospective matched control trial (n=60) conducted in India compared yoga in a naturopathic setting to standard Ayurvedic treatment over a ninety-day period [8]. The study indicated that the yoga group showed significant improvement in the reduction in pain (-5.1 $p<0.001$ VAS) and increased quality of life (+32.09 QoL Questionnaire).

Clinical finding

Yoga practice may decrease headache frequency, intensity and impact in individuals experiencing migraines.

A case report conducted in Germany with three subjects experiencing chronic migraines examined the impact of integrated migraine care including stress reduction, mindfulness and relaxation training, individualized nutritional advice, exercise guidance, hydrotherapy, acupuncture, and herbal medicine [12]. All three participants in the case studies demonstrated a decreased frequency and intensity of migraines. The case studies also indicated the need for each patient to become self-involved in their therapy to achieve clinical success. A single-case study conducted in USA involved a 45-year-old female with migraines, hypertension, pre-diabetes and a BMI of 30 kg/m2. The study involved an 8-week mindfulness training program lead by her naturopathic doctor and at the 11-week follow-up there was a significant decrease in both systolic and diastolic blood pressure (pre-meditation BL 149.2/97.3, Wk 11 114.5/68), migraine frequency and the ability to deal with caring for an ageing mother improved [10]. An uncontrolled study conducted in the USA (n=13) explored the impact of healing touch on chronic headaches. Following the intervention, 84.6% of the subjects showed improved frequency, intensity, and duration of pain with improvement ranging from 24 hours to 6 months, and 46% of the subjects indicated reduced need for medications and better relaxation and sleep [11].

Clinical finding

Hydrotherapy may reduce impact, frequency and intensity of headaches in individuals with chronic migraines already using standard pharmaceutical medications.

A randomized control trial conducted in India (n=40) compared the addition of hydrotherapy to pharmaceutical treatment of chronic migraines [9]. The hydrotherapy (HT) intervention (n=20) included hot arm and foot bath (103°F to 110°F) plus ice massage applied to the head along with standard pharmaceutical medication (Tx) (n=20). The intervention lasted 45 days with 20 minutes of daily treatment. The hydrotherapy group reported a reduction in the Headache Impact Test (HT -34.25, Tx -9.45, $p<0.001$), a reduction in pain frequency (HT -8.65, Tx -3.15, $p<0.001$), a reduction in pain intensity (HT -6.85, Tx -2.05, $p<0.001$) and a reduction in heart rate (HT -5.9, Tx +2.42, $p<0.05$).

Parkinson's Disease (PD)

Four studies researched Parkinson's Disease. Three of the studies from the USA examined the effects of intranasal reduced glutathione (GSH) [13-15] and one study from India explored complex naturopathic treatment which included electroacupuncture, dietary and lifestyle advice [16]. A cohort study conducted in the USA (n=15) prescribed 200 mg intranasal reduced glutathione for 45 minutes daily which led to significantly increased serum glutathione compared to baseline [14]. The other two studies were randomized trials that used a different dosing regimen and did not find any significant differences between intranasal reduced glutathione and placebo.

A single-case study conducted in India with a 56-year-old male diagnosed with stage III PD and presenting with slurred speech, right-sided bradykinesia, erectile dysfunction, rigidity, emotional instability, depression, postural instability, and a rating of 80% on the Schwab and England activities of daily living scale received 30-minute sessions of electroacupuncture 6 days/week, for 5 weeks [16]. Follow up assessment showed improvement in activities of daily living (-10 PDQ-39), improved balance (+2 Berg Balanced Scale) and a 20mmHg reduction in systolic blood pressure.

Other Neurological Conditions

Other neurological conditions researched in Germany, Egypt, India and the USA included ADHD [17-19], Alzheimer's disease [20, 21], autism spectrum disorders [22, 23], traumatic brain injury (TBI) [24, 25] and Transverse myelitis [26]. Five studies with a total population of 241 children with attention-related behavioural patterns or attention deficit hyperactive disorder addressed the following interventions – herbal medicine [19], omega-3 fish oils [18, 20, 21] and homeopathy [17]. A randomized controlled trial (n=144) conducted in Australia allocated participants to receive an omega-3 lipid extract of New Zealand green-lipped mussels or placebo for 14 weeks. [18]. While the study did not show any difference in the results of attention tests between groups, positive changes were observed in secondary outcome measures. These included increased mental performance including target memory ($p=0.04$), non-target memory ($p=0.02$) and picture recognition accuracy ($p=0.02$) based on the Computerised Mental Performance Assessment System. According to the Conners Parent Rating Scales, parents of participants in the intervention group also reported improvements, compared to placebo, in participants' symptoms such as hyperactivity (-10.2 vs-3.3, $p=0.04$), DSM inattention (-7.18, vs -3.3, $p=0.01$), DSM hyperactivity (-13.8 vs -4.1, $p=0.04$), learning problems (-5.9 vs -2.8, $p=0.05$) and impaired home life (-0.52 vs +0.05, $p=0.02$) with overall reduction in ADHD probability (-28.3 vs -13.1, $p=0.04$). However, participants in the intervention group also reported increased fatigue ($p=0.01$) while the placebo group reported reduced feelings of confusion ($p=0.01$).

Clinical finding

Omega-3 lipids may improve mental performance and reduce hyperactivity, inattention, learning problems and impaired home life in individuals with attention-deficit hyperactive disorder.

Two studies from the USA (n=441) explored the impact of fish oil on patients diagnosed with mild to moderate Alzheimer's disease [20, 21]. Participants in a placebo-controlled randomized study (n=39) conducted in the USA over 12 months were prescribed either omega 3 fish oil concentrate containing a daily dose of 675 mg DHA and 975 mg EPA or the same omega-3 fish oil concentrate plus alpha lipoic acid (ALA) at 600 mg per day [21]. Significant differences were seen in both treatment groups based on the Mini-Mental State Examination, with less cognitive decline observed in the active intervention groups when compared to placebo, and there was less decline in the Activities of Daily Living in both

treatment groups. Noticeable differences were observed in the combination treatment (omega-3 and ALA) when compared to placebo.

Clinical finding

Heavy metal chelation therapy may lessen maladaptive behaviours and increase adaptive behaviours as well as reduce total autism symptoms and severity in children with autism spectrum disorder.

A randomized control trial conducted in the USA involving 65 people with autism investigated the impact of heavy metal chelation therapy using meso-2,3-dimercaptosuccinic acid (DMSA) to aid the excretion of heavy metals and improve behaviours in children with autism [22, 23]. The study indicated that three rounds of DMSA resulted in increased excretion of toxic metals from baseline and normalized red blood cell glutathione and platelet counts [22]. Follow up analysis from this study also reported reduced occurrence of maladaptive behaviours [23]. After seven rounds of DMSA, there was a decrease in sensory/perceptual approach behaviours (-22%, $p<0.05$), ritualisms/resistance to change (-28%, $p<0.01$), arousal regulation problems (-22%, $p<0.01$), specific fears (-22%, $p<0.01$), and aggressiveness (-27%, $p<0.05$), with an overall reduction in the composite score of the Pervasive Developmental Disorder Behaviour Inventory – Maladaptive Behaviours (PDDBI-MB) of 24% ($p<0.001$). There was a concomitant increase in adaptive behaviours such as learning, memory and receptive language (+12%, $p<0.05$) but a corresponding decrease in social approach behaviours (-11%, $p<0.05$). Reductions were also observed in total autism symptoms measured by the Autism Treatment Evaluation Checklist (-26%, $p<0.001$) and symptom severity (Severity of Autism Scale: -19%, $p<0.001$).

A case study conducted in India reported the outcomes of a 32-year-old male who presented with transverse myelitis, paraplegia, sensory disturbances, pain, exertional dyspnea, poor sleep, emotional liability, and depression [8]. The patient received 15 sessions of 30 minutes of electro-acupuncture treatments daily over 3 weeks. By the end of treatment, the patient had significant improvement in quality of life across four domains of the WHO QoL BREF instrument: physical health (33 vs 94), psychological health (13 vs 56), social health (69 vs 75), and environmental health (14 vs 63). The patient also reported reduced insomnia (Pittsburgh Sleep Quality Index: 18 vs 9) and pain (VAS: 8 vs 1) as well as subjective improvement in symptoms such as dyspnea, fatigue, and ability to express happiness.

Table 24.1 Clinical research investigating neurological conditions conducted by naturopathic researchers

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Adams, et al. (2009) [USA, AMRO] [22] Adams, et al. (2009) [USA, AMRO] [23]	Randomized controlled trial	Autism spectrum disorders	Phase 1 & 2: dimercapto succinic acid (DMSA) 10 mg/kg TID or placebo	Phase 1: 3 days. Phase 2: 11 days	Placebo (topical cream)	106 Part A: 65 (31/33) Part B 2: 41 (26/15)	Urinary excretion of toxic metals after Phase 1 [BL to Dose 1, Dose 9]	**Increased urinary excretion** Lead: Dose 1 +713% ($p<0.001$) Dose 9 +638% ($p<0.001$) Tin: Dose 1 +241% ($p<0.001$) Dose 9 +314% ($p<0.05$) Bismuth: Dose 1 NS Dose 9 +128% ($p<0.05$) Uranium: Dose 1 +0.021 (<0.001) Dose2 +0.016 ($p<0.05$) Mercury Dose 1 +70% (<0.01) Dose 9 NS Titanium: Dose 1 +67% ($p<0.001$) Dose 9 +42% ($p<0.01$) Antimony: Dose 1 +49% ($p<0.05$) Dose 9 NS Tungsten: Dose 1 +51% ($p<0.01$) Dose 9 +18% ($p<0.05$) Nickel: Dose 1 -18% ($p<0.05$) Dose 9 NS Cadmium: Dose 1 NS Dose 9 NS Arsenic: Dose 1 NS Dose 9 -19% ($p<0.05$)

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Urinary excretion of toxic metals after Phase 2 [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Increased urinary excretion** Lead: Dose 1 +935% (p<0.001) Dose 9 +1562% (p<0.001) Round 2 +1001% (p<0.001) Round 4 +1063% (p<0.001) Round 6 +1005% (p<0.001) Tin: Dose 1 +118% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Bismuth: NS Uranium: NS Mercury: Dose 1, +120% (<0.05) Dose 9 NS Round 2 +98% Round 4 and 6 NS Titanium: Dose 1 +54% (p<0.01) Dose 9 +44% (p<0.05) Round 2, 4 and 6 NS Antimony: Dose 1 +49% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Tungsten: Dose 1 +51% (p<0.01) Dose 1 +18% (p<0.05) Round 2, 4 and 6 NS Nickel: Dose 1 -18% (p<0.05) Dose 9 NS Round 2, 4 and 6 NS Cadmium: Dose 1 NS Dose 9 -32% (p<0.05) Round 2, 4 and 6 NS Arsenic: Dose 1, NS Dose 9 -19% (p<0.05) Round 2 -39% (p<0.001) Round 4 -42% (p<0.001) Round 6 -31% (p<0.1)

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Red blood cell (RBC) Glutathione [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Normalized RBC glutathione**
							Platelet count [BL to Dose 1, Dose 9, Round 2, Round 4, Round 6]	**Normalized platelet counts**
							Pervasive Developmental Disorder Behavior Inventory (Maladaptive behaviors) [BL to Round 6]	**Reduced maladaptive behaviors** Sensory/Perceptual Approach Behaviors: 7 rounds -22% ($p<0.05$) 1 round -31% ($p<0.01$) Ritualisms/Resistance to Change: 7 rounds -28% ($p<0.01$) 1 round -23% ($p<0.01$) Arousal Regulation Problems: 7 rounds -22% ($p<0.01$) 1 round NS Specific fears: 7 rounds -22% ($p<0.01$) 1 round NS Aggressiveness: 7 rounds -27% ($p<0.05$) 1 round -26% ($p<0.05$) Social pragmatic problems: 7 rounds NS 1 round -29% ($p<0.01$) Semantic/Pragmatic problems: NS Composite: 7 rounds -24% ($p<0.001$) 1 round -24% ($p<0.001$)
							Pervasive Developmental Disorder Behavior Inventory (Adaptive behaviors) [BL to Round 6]	**Increased adaptive behaviors** Social approach behaviors: 7 rounds -11% ($p<0.05$) 1 round + 6% Express (Phonological and

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
								Semantic Pragmatic): 7 rounds +5% 1 round +17% (p<0.05) Learning, Memory and Receptive Language: 7 rounds +12% (p<0.05) 1 round +14% (p<0.05) Composite: 7 rounds +12% 1 round +11%
							Autism Treatment Evaluation Checklist [BL to Round 6]	**Reduced autism symptoms** SPLC: 7 rounds -21% (p<0.001) 1 round NS Sociability: 7 rounds -27% (p<0.001) 1 round -25% (p<0.05) Sensory/Cognitive Awareness: 7 rounds -27% (p<0.001) 1 round -26% (p<0.05) Health/Physical/Behaviors: 7 rounds -28% (p<0.01) 1 round NS Total: 7 rounds -26% (p<0.001) 1 round -19% (p<0.01)
							Severity of Autism Scale [BL to Round 6]	**Reduced autism severity** 7 rounds -19% (p<0.001) 1 round -18% (p<0.01)
							Autism Diagnostic Observation Schedule [BL to Round 6]	**Reduced autism symptoms** Communication: NS Sociability: 7 rounds -10% (p<0.01) 1 round NS Communication and sociability: 7 rounds -9% (p<0.001) 1 round NS Play: NS SBRI: NS

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Parent Global Impression [BL to Round 6]	NS
Arankalle, et al. (2013) [India, SEARO] [16]	Case report	Parkinson's Disease (stage III)	Electroacupuncture (specific points and scalp); dietary and lifestyle advice	4 weeks: 24 sessions over 4 weeks with 7-day rest period after 12 sessions.	Nil	1	Resting Heart rate (bpm) [BL to Wk 4]	**Reduced resting heart rate** – 4bpm
							Blood pressure (mmHg) [BL to Wk 4]	**Reduced blood pressure** Systolic: -20
							Berg Balance Scale [BL to Wk 4]	**Increased balance** +2
							Parkinson's Disease Questionaire-39 impact on quality of life [BL to Wk 4]	**Reduced impact on quality of life** -10
Geethanjali, et al (2016) [India, SEARO] [6]	Randomized controlled trial	Migraine without aura	Yogis kriyas – *Jaleneti* (saltwater nasal flush), *Vamanakriya* (water-induced self-emesis), *Kaplabhathi* (postures and breathing with back erect)	30 days – *Jaleneti:* 5 days in a week; *Vamanakriya:* 2 days in a week followed by *Kaplabhathi*	Waitlist	60 (30/30)	Migraine Disability Assessment score [BL to Dy 30]	**Reduced disability** Yoga: -13.0; Waitlist: -8.0 Between group: p<0.0001
							Pain Visual Analogue Score [BL to Dy 30]	**Reduced pain** Yoga: -3.2; Waitlist: -1.5 Between group: p=0.008
							Headache Impact Test [BL to Dy 30]	**Reduced impact** Yoga: -16.8; Waitlist: -12.1 Between group: p<0.0001
							Physical Health – WHO Quality of Life-BREF (WHO QoL-BREF) [BL to Dy 30]	**Increased physical health** Yoga: +35.9; Waitlist: +27.0 Between group: p<0.07
							Psychological Health – WHO QoL-BREF [BL to Dy 30]	NS
							Social relationships – WHO QoL-BREF [BL to Dy 30]	**Increased social relationships** Yoga: +9.9; Waitlist: +6.6 Between group: p<0.0001
							Environment – WHO QoL-BREF [BL to Dy 30]	**Increased environment** Yoga: +4.8; Waitlist: +2.8 Between group: p<0.0001
Haller, et al. (2015) [Germany, EURO] [24]	Case report	Traumatic Brain Injury	Inpatient treatment: craniosacral therapy (CST) and auricular acupuncture, cupping massage, hydrotherapy (cold affusions),	2 weeks: CST five 1-hour sessions	Nil	1	Visual Analogue Scale – Headache intensity [BL to Wk 2]	**Reduced intensity** 6-9cm to 2-4cm
							VAS – Vertigo [BL to Wk 2]	**Reduced vertigo** 6-10cm to 2cm

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
			Thermotherapy (hot and cold cataplasms), exercise, nutritional therapy, and phytotherapy with *Bryophyllum* species and *Avena sativa*. Relaxation, stress reduction, mindfulness, and cognitive restructuring training were also provided				CST assessment [BL to Wk 2]	**Increased** flexibility of cranial bones, atlanto-occipital joint leading to improved cervical rotation. **Reduced** tension in abdomen and neck muscles, release of sacrum and thoracic restrictions normalized posture and improved breathing, sleeping pattern, sensitivity to noise. Hands no longer numb
							General functioning/ well-being [BL to Wk 2]	**Increased wellbeing** Subjective 60% improvement, persisting at 6 months post treatment.
Jacobs, et al. (2005) [USA, AMRO] [17]	Randomized controlled trial (pilot)	Attention deficit-hyperactivity disorder (6 to 12 years)	Individualized single homeopathic remedy	6 weeks for 18 weeks	Placebo	43 (22/21)	Connors Global Index – Parents [BL to Wk 18]	NS
							Connors Global Index – Teacher [BL to Wk 18]	NS
							Connors Global Rating Scale – Revised [BL to Wk 18]	NS
							Continuous Performance Test [BL to Wk 18]	NS
Kean, et al. (2017) [Australia, WPRO] [18]	Randomized controlled trial	Attention deficit-hyperactivity disorder (6 to 14 years)	Omega-3 anti-inflammatory extract PCSO-524® (lipid extract of New Zealand green-lipped mussel)	14 weeks: QD	placebo	144 (74/70)	Test of Variables of Attention [BL to Wk 14]	NS
							Computerised Mental Performance Assessment System [BL to Wk 14]	**Increased mental performance** PCSO: Improved target memory (p=0.05) PCSO: Improved non-target memory (p=0.02) PCSO: Improved picture recognition accuracy (p=0.02)
							Brunel Mood Scale for adolescents [BL to Wk 14]	**Increased fatigue** PCSO: increased fatigue (p=0.01) Placebo: reduced feelings of confusion (p=0.01)

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Conners Parent Rating Scale [BL to Wk 14]	**Reduced parent-reported symptoms** Aggression NS Peer relations NS Global ADHD index NS Impaired school life NS Impaired relationships NS Inattention NS Conduct disorder NS Oppositional defiant disorder NS Executive function NS ADHD probability: PCSO -28.3; Placebo -13.1 Between group p=0.04 Impaired home life: PCSO -0.52; Placebo +0.05 Between group p=0.02 Hyperactivity: PCSO -10.2; Placebo -3.3 Between group p=0.04 DSM inattention: PCSO -7.18; Placebo -3.3 Between group p=0.01 DSM hyperactivity: PCSO -13.8; Placebo -4.1 Between group p=0.04 Learning problems: PCSO -5.9; Placebo -2.8 Between group p=0.05
Kisan, et al. (2014) [India, SEARO] [7]	Randomized controlled trial	Migraine (frequent, with or without aura)	Yoga (loosening and breathing exercises, *asanas*) and usual care	6 weeks: 1-hour sessions, five days a week	Usual care only	60 (30/30)	Headache impact test (HIT-6) [BL to Wk 6]	**Reduced impact** Yoga: -27.7 (p<0.001); Usual care: -6.8 (p<0.001) Between group: p<0.001
							Headache frequency (per Mth) [BL to Wk 6]	**Reduced frequency** Yoga: -9.5 (p<0.001); Usual care: -5.3 (p<0.001) Between group: p<0.001
							Visual Analogue Scale – Headache intensity [BL to Wk 6]	**Reduced intensity** Yoga: -6.67 (p<0.001); Usual care: -1.57 (p<0.001) Between group: p<0.001

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Self-perceived benefit scale [BL to Wk 6]	**'Greatly improved my clinical condition'** Yoga: 96.7%; Usual care: 30.0% **'More helpful than harmful'** Yoga: 100.0%; Usual care: 73.3%
							Heart rate [BL to Wk 6]	NS
							Heart rate variability (HRV) [BL to Wk 6]	NS
Lauche, et al. (2012) [Germany, EURO] [12]	Case reports	Chronic migraine	Integrative integrated migraine care (IIMC) 4 Modules that include integrated conventional medicine, physiotherapy, evidence- based complementary medicine and mind body therapy. (Acupuncture, cupping, hydrotherapy and different kinds of massage, TCM herbal medicine, regular exercise, relaxation training and mindfulness)	12 weeks (+ 6 and 12 month Follow up) Inpatient/ Outpatient care for 14 days; Day care for 6 hours, 1 day per week over 10 weeks	Nil	3	Migraine relief [BL to Wk 2, 6, Mth 6 and 12)	**Increased relief** Case 1: (outpatient) von Korff grade III migraine relief at first acupuncture session and ceased entirely by end of treatment Case 2: (outpatient) von Korff Grade not reported. Migraine relief at first acupuncture treatment and maintained. Follow -up MBSR course, six weeks post treatment migraines had return, declined for acupuncture management. Case 3: (outpatient) von Korff grade II. migraine frequency and intensity relieved by acupuncture, increased energy. Follow up 10 week, day care clinic.
Mischley, et al. (2015) [USA, AMRO] [13]	Randomized controlled trial (phase I/IIa)	Parkinson's Disease (Hoehn Yahr stage <3)	Intranasal reduced glutathione (GSH) 100mg and 200mg	12 weeks: 100mg TID 200mg TID	Control (saline) and placebo (watchful waiting)	34 (10/10/ 10/4)	Complete blood count [BL to Wk 12]	NS
							Alanine aminotransferase (ALT) [BL to Wk 12]	NS
							Aspartate aminotransferase (AST) [BL to Wk 12]	NS
							Blood urea nitrogen (BUN) [BL to Wk 12]	NS
							Creatine [BL to Wk 12]	NS
							Urinalysis [BL to Wk 12]	NS

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Monitoring of Side Effects Scale [BL to Wk 12]	NS
							SNOT-20 [BL to Wk 12]	NS
							Unified Parkinson's Disease Rating Scale (UPDRS) [BL to Wk 12]	Mild clinical improvements in both treatment arms compared to placebo (NS)
Mischley, et al. (2016) [USA, AMRO] [14]	Cohort	Parkinson's Disease	Intranasal reduced glutathione (GSH) 200mg	45 minutes (same time of day for each participant)	Nil	15	GSH and GSH/Cr concentrations (H-MRS) [BL to Min 45]	**Increased glutathione concentrations** GSH/Cr: +269% GSH: +240% 7.5 min: +0.03 (0.008-0.06) 19.9 min: +0.04 (0.01-0.08) 32.0 min: +0.04 (0.01-0.08) 44.7 min: +0.05 (0.01-0.11)
Mischley, et al. (2017) [USA AMRO] [15]	Randomized controlled trial	Parkinson's Disease (Hoehn Yahr stage 1-3)	Intranasal reduced glutathione (GSH) 100mg and 200mg TID	12 weeks: 100mg and 200mg TID (4-week washout period)	Control (saline)	39 (11/14/14)	Unified Parkinson's Disease Rating Scale (UPDRS) [BL to and Wk 4, 8, 12 and 16 (at same appointment time for each participant)]	NS
							GSH and GSH/Cr concentrations (H-MRS) [BL to and Wk 4, 8, 12 and 16]	NS trend toward increasing brain GSH concentrations in the 600 mg/d cohort
Mohamed, et al. (2017) [Egypt, EMRO] [25]	Non-randomized controlled trial	Severe Traumatic Brain Injury (STBI)	Clinical pathway (multidisciplinary care)	15 days	Control (usual care) routine nursing, medical and ancillary care in the trauma ICU of the hospital.	60 (30/30)	Complications related to hospitalization (patient #'s) [BL to day 15]	**Reduced complications** Fever (12 vs 24, p=0.04) (adjusted for age, NS) Procedural pain (0 vs 13, p=0.002) (adjusted for age, p=0.024) Hyperglycemia (4 vs 13, p=0.022) (adjusted for age, NS)
							Clinical variances [BL to day 15]	Most frequent variance were observed in nursing care (circulating air-cooling blankets, air matrices and graduated stockings, 4- day tracheostomy target) and professional consultation (rehabilitation and social worker)

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Invasive devices duration [BL to day 15]	**Reduced duration of invasive devices** Central venous catheter (-1.6, p=0.28)
							Length of ICU stay (# of days) [mean difference between groups]	**Reduced length of stay** (15 vs 17, p=0.07) (adjusted for age, p=0.009)
							ICU readmission rate (# of days) [mean difference between groups]	**Reduced readmission rate** (7 vs 13, p=0.001) (adjusted for age NS)
							Patient/family satisfaction in care structure and processes	**Increased satisfaction** 80-89%: 16 vs 0 70-79% 24 vs 0 60-69% 0 vs 13 <60% 0 vs 17 (p=0.01)
Mohanty and Shrestha (2017) [India, SEARO] [26]	Case report	Transverse Myelitis	Electroacupuncture	3 weeks: 15 x 30-minute treatments	Nil	1	WHO Brief QOL [BL to Day 21]	**Increased quality of life** Physical health (33 vs. 94) Psychological health (13 vs. 56) social health (69 vs 75) environmental health (14 vs. 63)
							Pittsburgh Sleep Quality Index [BL to Day 21]	**Reduced insomnia** 18 vs 9
							Visual Analogue Scale [BL to Day 21]	**Reduced pain** 8 vs. 1
							Disease-specific measure of subjective health status [BL to Day 21]	Not reported
Oberg, et al. (2013) [USA, AMRO] [10]	Case report	Migraine	Mindfulness meditation	8 weeks: self-directed program of 45 min sessions/wk	Nil	1	Blood pressure (BP), systolic/diastolic (pre- and post-meditation) [Weekly from Wk 1 to Wk 11]	**Reduced BP** Wk 1 BP: 149.2/97.3 vs. 132/84.6; Wk 11 BP: 114.5/68 vs. 112.7/72.7. Systolic (p<0.0001) Diastolic (p<0.0004)

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Migraine frequency (subjective) [BL to Wk 11]	**Reduced migraine frequency** Reduction until week 17 of migraine headache and use of associated medication
Quinn, et al. (2010) [USA, AMRO] [20]	Randomized controlled trial	Alzheimer disease (mild to moderate)	Algal-derived DHA 2g daily	18 months 2g daily	placebo	402 (238/164)	Alzheimer's Disease Assessment Scale [BL to Mth 18]	NS
							Clinical Dementia Rating [BL to Mth 18]	NS
							Mini-Mental State Examination [BL to Mth 18]	NS
							Alzheimer's Disease Cooperative Study activity of daily living scale [BL to Mth 18]	NS
							Neuropsychiatric inventory [BL to Mth 18]	NS
							Adverse events [BL to Mth 18]	NS
Sharma, et al. (2018) [India SEARO] [8]	Non-randomized controlled trial	Migraine headache (adults)	Yoga: *asana* postures, *pranayama* breathing, relaxation techniques, chanting	90 days: 40 min, daily for 1 week, then 5 days per week home practice until day 90	Control: usual care	60 (30/30)	Comprehensive Headache-related Quality of Life Questionnaire [BL to Dy 90]	**Increased quality of life** Yoga: +32.09; Usual care: -1.61 Between group: p<0.001
							Visual Analogue Scale [BL to Dy 90]	**Reduced pain** Yoga: -5.1; Usual care: +0.24 Between group: p<0.05
Shinto, et al. (2014) [USA, AMRO] [21]	Randomized controlled trial	Alzheimer's disease	Omega-3 fish oil concentrate containing a daily dose of 675mg DHA and 975mg EPA OR Omega-3 fish oil concentrate plus alpha-lipoic acid (ALA) 600 mg/day	12 months	placebo	39 (13/13/13)	Peripheral F2-isoprostane levels [BL to Mth 12]	NS
							Mini-Mental State Examination [BL to Mth 12]	**Reduced mental state** Omega-3: -4.3 Omega-3 + ALA: -1.0 Placebo: -4.6 Between group (Placebo vs ALA): p<0.01
							Activities of Daily Living [BL to Mth 12]	NS

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Instrumental Activities of Daily Living [BL to Mth 12]	**Increased activities** Omega-3: -0.7 Omega-3 + ALA: -0.9 Placebo: -4.2 Between group (Placebo vs ALA): p<0.01 Between group (Placebo vs Omega-3): p<0.01
Sujan, et al (2016) [India, SEARO] [9]	Randomized controlled trial	Chronic migraine	Hydrotherapy (hot arm and foot bath [103°F to 110°F]; ice massage to head) plus pharmaceutical medication	45 days; 20 minutes daily	Pharmaceutical medication only	40 (20/20)	Headache Impact Test [BL to Dy 45]	**Reduced impact** Hydrotherapy: -34.25 Pharmaceutical: -9.45 Between group: p<0.001
							Pain frequency (daily diary) [BL to Dy 45]	**Reduced pain frequency** Hydrotherapy: -8.65 Pharmaceutical: -3.15 Between group: p<0.001
							Visual Analogue Scale – intensity [BL to Dy 45]	**Reduced pain intensity** Hydrotherapy: -6.85 Pharmaceutical: -2.05 Between group: p<0.001
							Heart rate (beats per min) [BL to Dy 45]	**Reduced heart rate** Hydrotherapy: -5.9 Pharmaceutical: +2.42 Between group: p<0.05
							Standard Deviation of NN interval [BL to Dy 45]	NS
							Root mean square of the successive differences [BL to Dy 45]	NS
							Heart rate variability – total frequency (ms^2) [BL to Dy 45]	NS
							Low-frequency power (ms^2) [BL to Dy 45]	**No change** Hydrotherapy: -0.97 Pharmaceutical: -2.62 Between group: p<0.05

Author (year) [Country, world region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							High-frequency power (ms^2) [BL to Dy 45]	**Increased high-frequency power** Hydrotherapy: +1.28 Pharmaceutical: -0.80 Between group: $p<0.05$
							Low-frequency/ high-frequency ratio [BL to Dy 45]	**Reduced ratio between frequency** Hydrotherapy: -0.27 Pharmaceutical: -0.09 Between group: $p<0.01$
Sutherland (2009) [USA AMRO] [11]	cohort	Chronic headache	Healing Touch Therapy	3 weeks – minimum 3 treatment sessions 1 week apart, 30-40 minutes each.	Nil	13	Reduced duration of headaches, self-reported [BL to Wk 3]	**Reduced duration** 2 out of 13
							Reduced intensity of headaches, self-reported [BL to Wk 3]	**Reduced intensity** 12 out of 13
							Reduced frequency of headaches, self-reported [BL to Wk 3]	**Reduced frequency** 5 out of 13
							Reduced need for pain medication, self-reported [BL to Wk 3]	**Reduced need for pain medication** 6 out of 13
							Improved relaxation, self-reported [BL to Wk 3]	**Increased relaxation** 6 out of 13
							Improved sleep, self-reported [BL to Wk 3]	**Increased sleep** 5 out of 13
Weber, et al. (2008) [USA AMRO] [19]	Randomized controlled trial	Attention-Deficit Hyperactivity Disorder (Children and young adults 6 to 17yo who met DSM IV Edition criteria for ADHD by structured interview	8 weeks: 300mg of *Hypericum perforatum* standardized to 0.3% hypericin TID	8 weeks TID	Placebo	54 (27/27)	ADHD Rating Scale – IV [BL to Wk 8]	NS
							Clinical Global Impression Improvement Scale [BL to Wk 8]	NS
							Adverse effects	NS

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25 Skin Conditions

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HIGHLIGHTS

- Skin conditions are among the top 10 reasons patients seek naturopathic care.
- Naturopaths/NDs often treat common skin conditions such as acne vulgaris, dermatitis, dry skin, eczema, herpes simplex, herpes zoster, psoriasis, rosacea, urticaria and others.
- In naturopathic practice, the skin is viewed as an essential organ of detoxification and many skin conditions reflect internal imbalances or dysfunctions.
- Naturopaths/NDs use both internal and external therapies in the treatment of skin conditions.
- 62.5% of clinical studies investigating naturopathic treatments for skin conditions reported a positive outcome in at least one primary or secondary outcome measure.

The skin is a very complex organ with a vast array of functions. It is the largest organ in the body and from a naturopathic perspective, it is linked to and reflective of a person's inner state of health [1]. There are a diverse range of conditions that are associated with the skin such as common ailments: acne vulgaris, boils, bruises, burns, canker sores, conjunctivitis, dermatitis, eczema, herpes simplex (cold sores), pruritis, psoriasis, rosacea, urticaria, warts and more significant pathologies including herpes zoster (shingles), skin cancers, pemphigus vulgaris, and yeast infections.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=8) focused on skin conditions conducted by naturopathic researchers. This research includes a total of 92 participants and was conducted in the United States of America (USA) (n=3), Canada (n=2), India (n=2) and Australia (n=1). The research includes case reports/series (n=5), uncontrolled trials (n=2), and a randomized clinical trial (n=1). Herbal medicine (n=4) was the most studied intervention of which two studies involved ingestible herbal medicine, two the topical application of herbs, and one provided herbal medicine along with homeopathy. Other interventions were clinical nutrition (n=2), and a complex naturopathic intervention including dietary fasting along with generally naturopathic care and yoga (n=1).

The skin conditions examined in these studies include acne (n=3), vitiligo (n=1), psoriasis (n=1), dermatitis (n=1), plantar warts (n=1), and a facial rash (n=1). Of all the naturopathic clinical studies examining skin condition populations, 100% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 25.1: Original research on skin conditions conducted by naturopathic researchers.*

Implications

Skin conditions are listed in the top primary health conditions for which individuals consult with a naturopath/naturopathic doctor [2]. They are also the fourth leading cause of non-fatal disease burden globally [3], with multidimensional psychological, social and financial consequences as well as clinical implications [4]. Based on these preliminary results, a variety of naturopathic treatments may have clinical benefit for a diverse range of skin conditions. The majority (62.5%) of the naturopathic research studies on skin conditions involves case reports or case studies. Although all studies indicated positive outcomes, naturopathic research focused on dermatological conditions needs to be expanded.

The unique perspective of skin as a detoxification organ of the body and naturopaths/naturopathic doctors broad treatment approach when managing skin conditions also warrant consideration. The naturopathic Emunctory Theory (outlined further in Chapter 3) states that proper elimination of toxins is essential to overall health and that eliminating toxins is often the first required treatment focus, especially for chronic disease.

Elimination of toxins assists vitality and its corollary, lack of elimination blocks vitality or vital force. The primary emunctory pathways include the lungs (breath), kidneys (urine), bowels (stool), skin (sweating), menses/ejaculation and voice (speaking) [1]. Not only do naturopaths/naturopathic doctors acknowledge the importance of healthy skin for overall physical health, but equally the naturopathic approach recognizes that skin conditions often manifest due to dysfunction in other organs and systems. As an example, an international survey has found naturopaths/naturopathic doctors are more likely to consider the digestive system or endocrine system as important factors when providing care to patients presenting with skin conditions as their primary concern [5]. Naturopathic care for skin conditions often involves interventions that address a patient's internal state of health and topical interventions to address the manifestation of the skin condition.

The perspective and naturopathic approach to skin conditions have results in an expanded understanding of the role of the gastrointestinal system [6], the nervous system [7], the environment [8], immune function [9] and nutritional status [10] on skin health with much of this contribution considering the inter-relationship of more than one of these factors on the pathogenesis and treatment of skin conditions [6-8, 10]. As such, research examining naturopathic treatment of skin conditions needs to reflect the complexity with which naturopaths/naturopathic doctors approach this important organ.

Studies based on specific conditions:

Acne vulgaris

Three studies, conducted in India, the USA and Canada, examined naturopathic interventions in the treatment of acne. Two of these were case reports and one an uncontrolled trial. The interventions included general naturopathic care (dietary interventions, hydrotherapy, and yoga) [11], human monoclonal antibody MABp1 [12] and vitamin-mineral supplementation [13]. All studies showed significant results. The case report conducted in Canada presented the results of a series of five cases treated over approximately two months [13]. The patients were prescribed daily intake of a multi-nutrient formula containing essential fatty acids (EPA, 1000mg), zinc gluconate (15mg), selenium (200mcg), chromium (200mcg) and epigallocatechin-3-gallate from green tea (200g). After treatment, the patients had an average decrease of 40 acne lesions and 15 inflammatory papules. They also had an average score increase of 24% across all domains on the Arizona Integrative Outcomes Scale.

Psoriasis

A randomized controlled trial conducted in India (n=60) investigated the effectiveness of a starch-fortified turmeric bath combined with other naturopathic interventions including diet therapy, massage, yoga and hydrotherapy in the treatment of psoriasis [14]. The turmeric bath intervention group were compared with a group receiving the other naturopathic interventions but without the turmeric bath. Both groups received treatment for 10 days and, while both groups had a reduction in Psoriasis Area and Severity Index scores, a significantly greater reduction was reported for the turmeric bath group (-13.9 vs -0.15, $p<0.01$).

Clinical finding

Hydrotherapy involving a turmeric bath may reduce the symptoms and severity of psoriasis.

Vitiligo vulgaris

A single-armed clinical trial conducted in Canada investigated *Ginkgo biloba* as a treatment for Vitiligo vulgaris in 12- to 35-year-olds (n=12) [15]. Participants were administered one capsule containing 60mg of standardized *Ginkgo biloba* twice per day for 12 weeks. Compared to baseline, the participants reported changes in both outcome measures. The Vitiligo Area Scoring Index reduced by -0.05 ($p=0.02$) and the disease activity domain of the Vitiligo European Task Force Score reduced by -3.9 ($p<0.001$) with no change in the area or staging domains.

Other skin conditions

Three remaining studies investigated herbal and homeopathic intervention in the management of topical steroid refractory dermatitis [16]; a herbal intervention for plantar warts demonstrating total resolution at day 90 [17]; and an unknown skin condition was managed with herbal medicine with a focus on nervous system support over 6 weeks resulting in reduced lesions (-36%), improved digestive symptoms, reduced anxiety and decreased perception of negative body image [7].

Table 25.1 Clinical research investigating skin conditions conducted by naturopathic researchers

Author (date) [Country, World region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Ameya and Nair (2017) [India, SEARO] [11]	Case report	Acne vulgaris	Day 1 to 5: Diet plan including Holy Basil decoction, fresh carrot juice, mosambi (sweet lime) juice, non-spicy vegetably curry and bhakri (sorghum preparation). Day 6 to 16: Alternating daily between therapeutic fasting, and lemon honey juice and tender coconut water. Swedish massage, steam bath, warm water enema and hip bath. Yoga 45 minutes per day on non-fasting days	16 days (+14 and 30 day follow up)	Nil	1	Acne lesions and inflammation (BL to Dy 30, 60]	**Reduced lesions and inflammation** Dy 30: noticeable reduction in lesions, with no noticeable inflammation or swelling Dy 60: No relapse of symptoms reported.
Canavan and Yarnell (2005) [USA, AMRO] [16]	Case report	Dermatitis not responsive to topical steroids (51-year-old white healthy female)	(1) Initial treatment: chlorine/water wash (2) Second treatment: *Calendula officinalis* and *Ocimum tenuiflorum* ointment, homeopathic rhus toxicodendron 30C (3) Third treatment: topical corticosteroid (specific drug and concentration unknown), homeopathic causticum 30C and arsenicum album 30C (4) Fourth treatment: *Impatiens capensis* tincture and *Calendula officinalis* cream topically, homeopathic sulfur 30C (5) Fifth treatment: *Grindelia spp* tincture topically and *Grindelia spp/Calendula officinalis* cream	(1) unknown (2) unknown (3) unknown (4) several applications of cream (timeline unknown) (5) applied 25hr after (4) within 1 week affected areas resolved	Nil	1	Skin area affected by rash, self- and physician-assessed	**Reduced affected area** 1: reduction on left arm, no change on right 2: spread from arms to supra-pubic region, lower legs, and forearms 3: stable 4: stable 5: rash area stopped oozing and shrank gradually to total resolution

Author (date) [Country, World region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Carrasco, et al (2015) [USA, AMRO] [12]	Uncontrolled trial	Acne vulgaris with psychiatric comorbidity	True human monoclonal antibody MABp1	6 weeks	Nil	11	Inflammatory lesion counts [BL to Wk 6]	**Reduced lesions** -36%
							Hospital Anxiety and Depression Scale [BL to Wk 6]	**Reduced anxiety** Anxiety: -5 Depression: NS
							Body Image Disturbance Score [BL to Wk 6]	**Reduced negative body image** -0.2
Gerontakos and Casteleijn (2018) [Australia, WPRO] [7]	Case report	Facial skin condition (unknown atiology) association to nervous system	Herbal medicine *(Avena sativa, Cynara scolymus, Passiflora incarnata, Asparagus racemosus. Zingiber officinale, Gentian luteum. Ulmus rubra)* plus daily mediation and Australian Bush Flower Essence	6-10 weeks	Nil	1	Presentation of skin condition; digestion (presence of constipation and/or bloating); mental well-being (perceived stress levels)	**Reduced symptoms** At 10 weeks there was no return of skin condition. Improved digestive symptoms at 4 weeks. Patient self-reported association of skin condition with stress and mental and physical wellbeing.
Nelson, et al. (2017) [USA, AMRO] [17]	Case report	Plantar warts of the left hallux unresponsive to cryotherapy	*Hypericum perforatum* aerial parts 2.5%, *Lavandula officinalis* leaf 10%, *Glycyrrhiza glabra* root 2.5%, *Melissa officinalis* leaf 6%, *Eleutherococcus senticosus* root 4%, and *Sarracenia* spp. aerial parts 25% gel with allantoin applied 1 – 2 times daily after application of a pumice stone to the lesions	63 days (+ 30 days follow-up)	Nil	1	Extent of visible lesion	**Reduced lesions** *Day 5:* 'remarkable' reduction *Day 17:* return of epidermal ridges in the affected toe *Day 27:* no further progress *Day 36:* no further progress *Day 46:* appearance of keratotic debris and superficial epidermal necrosis *Day 56:* same as day 46 *Day 63:* changes from day 46 resolved, wart largely resolved; benign, painless petechial hemorrhages on medial margin *Day 90:* total resolution
Rubin, et al. (2008) [Canada, AMRO] [13]	Case report	Acne vulgaris	1000 mg of EPA (from sardines and anchovies), zinc gluconate 15mg, selenium 200 mcg, chromium 200 mcg and epigallocatechin-3-gallate (EGCG) 200 mg (from green tea extract)	2 months minimum	Nil	5	Inflammatory acne lesions	**Reduced lesions** Lesions (average): -40 Inflammatory papule lesions (average): -15
							Arizona Integrative Outcomes Scale	**Improved outcomes** +24% average across domains

Author (date) [Country, World region]	Design	Study Population	Intervention	Dose and Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Shathirapathiy et al. (2015) [India, SEARO] [14]	Randomized clinical trial	Psoriasis	Starch-fortified turmeric bath with naturopathy interventions (massage, yoga, hydrotherapy, diet therapy)	10 days	Naturopathy interventions (massage, yoga, hydrotherapy, diet therapy)	60 (30/30)	Psoriasis Area and Severity Index [BL to Dy 10]	**Reduced severity** Turmeric Bath: -13.9 Naturopathy only: -0.15 Between group: p<0.01
Szczurko, et al. (2011) [Canada, AMRO] [15]	Uncontrolled trial	Vitiligo vulgaris (12 – 35 years)	Ginkgo biloba 60mg (standardised to 15mg gingkoflavonglycosides and 4mg terpene lactones per pill), 1 capsule twice per day	12 weeks	Nil	12	Vitiligo Area Scoring Index [BL to Wk 12]	**Reduced area** Total: -0.05 (p=0.02)
							Vitiligo European Task Force Score [BL to Wk 12]	**Reduced disease activity** Area: NS Staging: NS Disease activity: -3.9 (p<0.001)

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26 Women's Health Conditions

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HIGHLIGHTS

- Women represent over 70% of the patients that seek naturopathic care.
- Women's health concerns affect a substantial proportion of the population and include premenstrual syndrome, polycystic ovarian syndrome, endometriosis and problematic symptoms associated with reproductive life stages such as pregnancy, childbirth, and menopause or perimenopause.
- The holistic person-centered approach of naturopathic care is well suited to addressing women's health concerns.
- Naturopaths/NDs use a wide range of therapies in treating women's health concerns.
- 81.8% of clinical studies investigating naturopathic treatments for skin conditions reported a positive outcome in at least one primary or secondary outcome measure.

Female reproductive health conditions include illnesses such as endometriosis and urinary tract infections; syndromes such as premenstrual syndrome and polycystic ovarian syndrome; and reproductive life stages which may cause problematic symptoms for some women, such as pregnancy, childbirth, and menopause or perimenopause. Women's health conditions impact a substantial proportion of the global population, with at least three quarters of women experiencing painful menstruation [1] and menopausal symptoms [2] alone. Historically women's health concerns have not been well represented in allopathic medical practice or research, with women's complaints routinely dismissed, and female participants largely absent from clinical research [3].

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=11) naturopathic clinicians undertook in the field of women's health conditions. This research includes a total of 1,196 participants and was conducted in Australia (n=6), India (n=3), the United States of America (USA) (n=1), and Canada (n=1). The study designs include randomized control trials (n=8), case reports (n=2) and an uncontrolled trial (n=1). The studied interventions featured a range of therapeutics including herbal medicine (n=6) dietary and lifestyle changes (n=3), acupuncture (n=2), hydrotherapy (n=2), and yoga (n=1) and included five studies that employed interventions involving more than one therapeutic category.

The women's health conditions examined in these studies include menopausal symptoms (n=4), menstrual disorders (n=2), polycystic ovarian syndrome (n=2), candidiasis (n=1), interstitial cystitis (n=1), and recurrent pregnancy loss (n=1). Of all the naturopathic clinical studies examining women's health populations, 81.8% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 26.1: Clinical research investigating women's health conditions conducted by naturopathic researchers.* This body of naturopathic research on women's health conditions is also supported by more than 40 observational studies and more than 30 reviews or meta-analysis conducted by naturopathic researchers on this topic, as outlined in Chapter 28.

Implications

Female reproductive health conditions are diverse in etiology, pathophysiology, and symptomatology and are listed in the top five primary health condition for which individuals consult with a naturopath/naturopathic doctor [4]. Females are more likely than men to consult with a naturopath/naturopathic doctor and represent approximately three quarters of naturopathic patients. This includes women with chronic pelvic pain [5], women attempting to conceive [6], pregnant women [7] and women experiencing menopausal symptoms [8]. Naturopathic research indicates that the types of conditions for which women seek naturopathic care may benefit from naturopathic clinical treatments.

The most common female reproductive health conditions reported by patients seeking naturopathic care are dysmenorrhea and other menstrual complaints, polycystic ovarian syndrome and endometriosis, as well as support during menopause/perimenopause, preconception, pregnancy, and the postnatal period [4, 9]. The naturopathic focus on wellness, health promotion and disease prevention, working with the healing power of nature, and providing care to the whole person is particularly important for these women as it enables naturopaths/naturopathic doctors to support women during these normal life stages with a focus on health and wellness rather than illness. Moreover, women with reproductive health care needs commonly report valuing holistic care that is empowering and acknowledges their experiences and the impact of any symptoms on their quality of life [10-12]; features that characterize patient experiences of naturopathic care [13, 14].

Women with reproductive disorders such as those investigated in the naturopathic research also report being dissatisfied with the standard medical treatment and care options available to them (e.g. polycystic ovarian syndrome [15], interstitial cystitis [16, 17]). Given the positive outcomes identified for these conditions, naturopathic treatments are a valuable addition to the available treatments for women. To date, the research has primarily focused on herbal and dietary interventions with herbal treatments having the most notable clinical effects. It is also interesting to note that several herbal interventions employed multi-botanical formulas and, in some instances, combined herbal treatments with dietary and lifestyle changes. These characteristics of naturopathic treatments highlight naturopaths'/naturopathic doctors' application of complex, whole person treatments for women's health conditions.

As such, women's health is an important focus area for both naturopathic practice and naturopathic research. In part, this may be driven by the number of women seeking naturopathic care due to the high proportion of the naturopathic workforce in some countries that are female [18], and the appeal of the egalitarian, empowering and holistic model of care that characterizes naturopathic consultations [19]. Specifically, naturopathic consultations are, on average, 30 minutes to one hour in duration and this time is dedicated to collecting a range of information vital to undertaking a naturopathic assessment including understanding the patient's mental and emotional status and sense of wellbeing (see Chapter 1). These features provide support to the patient that extends beyond the immediate issues associated with their primary complaint and may facilitate whole-person healing [20]. Given the high proportion of women consulting with a naturopath/naturopathic doctor internationally, and the needs of women's health in conventional medicine, the results of these studies highlight the potential contribution of naturopathic care to women's health in the community and the need for further research.

Studies based on specific conditions:

Menopausal symptoms

Four studies, three from Australia and one from the USA, sampled women experiencing menopausal symptoms [21-24] with a primary focus on vasomotor symptoms (e.g., hot flushes, night sweats). Three studies examined the effects of a herbal medicine product [22-24], two of which constituted a combination of herbal medicines [22, 23] and one contained a single herbal medicine [24]. One of the herbal medicine studies also included a study arm in which dietary changes were studied [22]. A further study tested the effects of acupuncture on menopausal symptoms [21].

Clinical finding

Fenugreek *(Trigonella foenum-graecum)* may reduce symptoms of menopause.

A randomized controlled trial conducted in Australia (n=104) of women 40-65 years old, experiencing menopausal/perimenopausal symptoms examined the effects of a proprietary herbal medicine product containing 300mg of *Trigonella foenum-graecum* L. (fenugreek) de-husked seed extract, standardized for a minimum of 50% content of forustanol saponins [24]. Participants in the intervention group (n=54) ingested one capsule twice daily, delivering an equivalent of 600mg/day of *Trigonella foenum-graecum*, for 12 weeks. Their results were compared with participants (n=50) using a maltodextrin capsule placebo. The study outcomes were measured by the change from baseline in Menopause-Specific Quality of Life (MENQOL) questionnaire scores at Week 4, 8 and 12. Women in the intervention group had lower symptom scores, indicating reduced symptoms, across all domains of MENQOL – vasomotor, psychosocial, physical, sexual and total quality of life – at all time points compared to baseline. Compared with the placebo group, these reductions in menopausal symptoms were statistically significant for all domains ($p<0.001$).

A second randomized controlled trial conducted in Australian study of women (n=104) experiencing menopausal symptoms scoring greater than 'mild' on MENQOL examined the effects of a multi-botanical capsule comprising of 100mg *Tinospora cardiofolia* (stem), 100mg *Asparagus racemosus* (root), 100mg *Withania somnifera* (root) and 225mg *Commiphora mukul* (gum exudate) [22, 23]. Throughout the study period of 12 weeks, participants in the intervention group (n=54) ingested

one capsule twice daily and the placebo group (n=50) were given an identical capsule containing maltodextrin. Similar to the previous study, change from baseline at Week 4, 8 and 12 for all symptom domains of the MENQOL questionnaire was used to measure study outcomes. A statistically significant difference in change in symptom scores for each domain was reported between groups, with a greater reduction in symptoms reported for the intervention group compared to placebo ($p \leqslant 0.002$). The study also measured changes from baseline in the 7-day incidence of hot flushes, night sweats and total vasomotor symptoms at Week 4, 8 and 12. The intervention group reported a reduction in hot flushes (-30%), night sweats (-50%), and total vasomotor symptoms (-43%) at Week 4, and these reductions increased in magnitude through to Week 12 (Hot flushes: -64%; night sweats: -71%; total flushes: -67%). The difference in change in 7-day incidence of vasomotor symptoms between the intervention and placebo groups was statistically significant across all time points for all symptom categories ($p<0.001$). Safety data collected in this study found no difference between groups.

Clinical finding

A combination herbal medicine containing *Tinospora cardiofolia, Asparagus racemosus, Withania somnifera* and *Commiphora mukul* may reduce hot flushes and night sweats in women experiencing menopausal symptoms.

Menstrual disorders

Two studies investigated the potential impact on primary dysmenorrhea with hydrotherapy and acupuncture [25, 26]. An uncontrolled pilot study conducted in India examined the use of hydrotherapy in the form of a hot hip-bath immersion from day 20 of the menstrual cycle. The study measured the effects of the hydrotherapy intervention on menstrual pain, absenteeism from work and non-steroidal anti-inflammatory drug (NSAID) use over a three month period [25]. Participants reported being absent from work between seven and eight days fewer per month and having a reduction in pain on the first day of the period (month 1 -2.7, month 2 -2.8 and month 3 -3.2 points) based on a Visual Analogue Scale. They also reported a concomitant reduction in use of NSAID use over the same time.

A randomized controlled trial conducted in India evaluated an acupuncture protocol in a naturopathic setting on pain, muscle cramping, and systemic symptoms (e.g., headache, nausea, mood changes) over a 90-day period [26]. The study utilizing acupuncture as a treatment approach recruited women between the ages of 17-23 years [26]. Participants were required to have a history of primary dysmenorrhea for at least 1- year, regular periods and no use of contraceptive devices or pills and no pain medication use for 6 months prior to the commencement of the study. Participants were randomized to either the study group (n=30) or control (n=30) and assessments for pain intensity, muscle cramping and systemic symptoms (headache, dizziness, diarrhea, faint feeling, mood changes, tiredness, nausea and vomiting) were conducted at baseline (Day 1), Day 30, Day 60 and Day 90. A 12-point acupuncture protocol was used, and needles were in place for 20 minutes/session. Each participant in the intervention group received 45 acupuncture sessions (15 sessions in 30 days over 90 days), while the control group received no treatment. Results of the treatment demonstrated a significant reduction in all outcome measures at Day 30, Day 60, and Day 90 except for headaches, which was only significant after the intervention period. None of participants reported adverse effects during the study.

Clinical finding

Acupuncture may reduce pain intensity, muscle cramping, and other systemic symptoms in individuals with primary dysmenorrhea.

Polycystic Ovarian Syndrome

Two studies, one from Australia and one from India, examined outcomes of complex interventions for women with polycystic ovarian syndrome (PCOS) [27, 28].

The randomized controlled trial conducted in Australia sampled women (n=122) between 18 and 44 years old with PCOS diagnosis confirmed according to the Rotterdam criteria [27, 28]. The study compared a lifestyle intervention with a combined lifestyle and herbal intervention for three months. The lifestyle intervention consisted of lifestyle counselling, inclusive of dietary and exercise behaviours, delivered through a structured personalized plan and fortnightly follow-up support. The herbal medicine intervention constituted administration of two herbal medicine products: (1) Three tablets administered daily containing combined extracts equivalent to 750mg *Glychyrrhiza glabra* (root), 750mg *Paeonia lactiflora* (root), 750 mg *Cinnamomum verum* (stem bark) and 750mg *Hypericum perforatum* (flowering herb); (2) Three tablets per day for ten consecutive days – commencing either on Day 5 of the menstrual cycle of women with oligomenorrhea or within one week of trial commencement for women with amenorrhea- containing a single herbal extract equivalent to 13 500mg *Tribulus terrestris* (aerial parts) standardized to 100 mg furostanol saponins (protodioscin). There were 60 participants in the herbal

and lifestyle (HL) intervention arm and 62 participants in the lifestyle only (LO) arm. At the end of the 3-month study period, a significant ($p<0.01$) difference in number of days between menstrual periods (Mean difference: -42.9 days), body weight (-2.95 kg), body mass index (-1.0), waist circumference (-3.41 cm) in favor of the HL group compared to LO was reported. Comparatively greater reductions in luteinizing hormone (-1.82 IU/L), fasting insulin (-0.44 mU/L) and systolic (-3.6 mmHg) and diastolic (-5.13) blood pressure, as well as increased estradiol (+68.9 pmol/L) were also reported in the HL group. The quality-of-life scores, as measured by the Polycystic Ovarian Syndrome Questionnaire (PCOSQ), were also lower in the HL group compared with the LO group, indicating an improved quality of life in participants receiving HL. Depression, anxiety, and stress levels were also significantly reduced for participants in the HL group compared to those receiving LO. There was no difference in the proportional rates of miscarriage reported between groups, but pregnancy rates were higher (RR 3.9) for women in the HL group compared with the control.

Clinical finding

Naturopathic care involving individualised lifestyle modification, dietary counselling, and herbal medicine may reduce menstrual irregularity, body weight, waist circumference, depression, anxiety while improving hormone levels, blood pressure and quality of life in individuals with polycystic ovarian syndrome.

Other women's health conditions

Three additional studies two from Australia and one from Canada investigated the use of herbal medicines for other women's health conditions: the first for recurrent pregnancy loss [29], the second as an aid in the resolution of vaginal candidiasis [30], and the third for the treatment of interstitial candidiasis [31].

A randomized double blind placebo control trial conducted in Australia sought to investigate the efficacy of garlic tablets (Garlicin™ tablets at 3 tablets, twice per day [equivalent to 2100mg garlic powder, 19.2mg allicin]) on vaginal colony counts of candida in the two week prior to menstruation in asymptomatic women with colonized *Candida spp* (n=59) [30]. The outcomes were 1) the proportion of cases where women with Candida colony counts >100 CFU/ml in any given day during the last 7 days before menstruation, 2) quantitative counts of *Candida spp.* on daily vaginal swabs taken 2 weeks prior to menstruation, 3) itch (mild, moderate, severe) and 4) abnormal discharge (Yes/No). Sixty-three eligible women were randomized into the trial and 59 completed the study. No differences in the proportion of "cases" within the garlic group versus the placebo group. No difference in quantitative vaginal counts (daily swabs) or symptoms (itch and vaginal discharge) was found between the two groups. The study was powered to identify a 40% effect size between the treated and control, whereas a smaller effect size of 14% was achieved.

A case report conducted in Canada presented the outcome of the use of *Vitex agnus-castus* during the first trimester of pregnancy [29]. A woman with a history of recurrent pregnancy loss and demonstrated low progesterone levels (22.1 nm/L [1st trimester normal range: 18-250 nm/L]) was given 166.6 mg of 6:1 *Vitex agnus-castus* fruit extract from 1000 mg of fruit per day. After one month, a home pregnancy test was positive. Subsequent laboratory and ultrasound assessments at 5 weeks plus 2 days confirmed bHCG of 1200 IU/ml and progesterone of 85 nm/L and a singleton uterine pregnancy. The patient's obstetrician/gynecologist recommended discontinuation of the *Vitex agnus-castus* and prescribed progesterone suppositories. Subsequent ultrasounds and screening testing were normal, and the patient had a healthy pregnancy, resulting in the delivery of a full-term infant. At 15 months postpartum, the *Vitex agnus-castus* was restarted and one month later a second pregnancy was confirmed via a positive pregnancy test. The *Vitex agnus-castus* was continued until the 8th week of pregnancy and then discontinued. Ultrasounds at weeks 12, 20 and 28 reveal a healthy singleton uterine pregnancy. At the time of publication, the patient was 38 weeks pregnant.

Table 26.1 Clinical research investigating women's health conditions conducted by naturopathic researchers

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Arentz, et al. (2017) [Australia, WPRO] [27]	Randomized controlled trial	Polycystic ovarian syndrome (Women, 18-44 years, BMI >24.5 kg/m^2)	Herbal medicine: Tableted extracts of *Glycyrrhiza glabra* root 2.25 g, *Paeonia lactiflora* root without bark 2.25 g, *Cinnamomum verum* bark 2.25 g, *Hypericum perforatum* flowering tops 2.25 g (throughout the cycle), *Tribulus terrestris* aerial parts (standardized to 110 mg protodioscin/tablet) 40.5 g (follicular phase of menstrual cycle only) once per day. Lifestyle change: calorie-controlled, low-glycemic, nutrient-dense diet; 150 min exercise per week including 90 min aerobic activity (60 – 90% of maximum heart rate) with optional occasional supervised exercise sessions	3 months	Lifestyle change only	122 (60/62)	Time between menstrual periods (days) [BL to Mth 3]	**Reduced time between menstrual periods** Herbal and Lifestyle: 63.7 Lifestyle only: 106.6 Between group: p<0.01
							Women with normal menstrual cycle length defined as 20 – 34 days (%) [BL to Mth 3]	**Increased proportion** Herbal and Lifestyle: 55% Lifestyle only: 24.2% Between group: p<0.01
							Body weight (kg) [BL to Mth 3]	**Reduced body weight** Herbal and Lifestyle: 90.2 Lifestyle only: 97.2 Between group: p<0.01
							Body mass index (kg/m^2) [BL to Mth 3]	**Reduced body mass index** Herbal and Lifestyle: 33 Lifestyle only: 35 Between group: p<0.01
							Waist-to-hip ratio [BL to Mth 3]	NS
							Serum luteinizing hormone (LH) level (IU/L) [BL to Mth 3]	**Reduced LH** Herbal and Lifestyle: 5.84 Lifestyle only: 7.4 Between group: p=0.04
							Serum FSH (IU/L) [BL to Mth 3]	NS
							Serum estradiol (pmol/L) [BL to Mth 3]	**Increased estradiol** Herbal and Lifestyle: 217 Lifestyle only: 148.1 Between group: p=0.03
							Serum testosterone, total (nmol/L) [BL to Mth 3]	NS
							Serum sex hormone-binding globulin (nmol/L) [BL to Mth 3]	NS
							Serum fasting glucose (nmol/L) [BL to Mth 3]	NS

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Serum insulin (mU/L) [BL to Mth 3]	**Reduced insulin** Herbal and Lifestyle: 12.3 Lifestyle only: 20.3 Between group: p=0.02
							Blood pressure (BP), systolic (mmHg) [BL to Mth 3]	**Reduced BP** Herbal and Lifestyle: 114.3 Lifestyle only: 118 Between group: p=0.01
							Blood pressure (BP), diastolic (mmHg) [BL to Mth 3]	**Reduced BP** Herbal and Lifestyle: 69.3 Lifestyle only: 74.6 Between group: p<0.01
							Impact on health-related quality of life (total PCOS score) [BL to Mth 3]	**Reduced impact** Herbal and Lifestyle: 81.5 Lifestyle only: 109.3 Between group: p<0.01
							Depression, Anxiety and Stress Scale [BL to Mth 3]	**Reduced depression** Herbal and Lifestyle: 3.5 Lifestyle only: 7.5 Between group: p<0.01 Reduced anxiety Herbal and Lifestyle: 2.4 Lifestyle only: 6.3 Between group: p<0.01 Reduced stress Herbal and Lifestyle: 4.9 Lifestyle only: 9.6 Between group: p<0.01
Aucoin (2018) [Canada, AMRO] [29]	Case report	Recurrent pregnancy loss (Female, 29 years)	*Vitex agnus-castus* fruit extract 166.6 mg, 2 capsules per day (fifth and six pregnancies) Progesterone 200 mg vaginal pessary twice daily (from week 5 to week 10 of fifth pregnancy only)	First trimester for two consecutive pregnancies	First pregnancy on presentation (fourth pregnancy in case received no treatment)	1	Serum β-human chorionic gonadotropic (HcG) (IU/ml)	**Increased HcG** 4th pregnancy: 459 5th pregnancy: 1200 6th pregnancy: Not reported

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Serum progesterone (nmol/ml)	**Increased progesterone** 4th pregnancy: 22.1 5th pregnancy: 85.0 6th pregnancy: not reported
							Pregnancy outcome	**Live births** 4th pregnancy: spontaneous abortion at 5 weeks, 6 days 5th pregnancy: full-term live birth 6th pregnancy: 38 weeks' pregnancy with normal, live, singleton expected
Bharthis, et al. (2012) [India, SEARO] [25]	Uncontrolled trial	Primary dysmenorrhea	Hot hip bath with cold compress on the head	3 menstrual cycles + 2 months follow-up	Nil	17	Absenteeism due to pain (days) [BL to Mth 5]	**Reduced absentees** Mth 1: -7 ($p < 0.01$) Mth 2: -8 ($p<0.01$) Mth 3: -8 ($p<0.01$)
							Pain on before onset of menstruation, Visual Analogue Score [BL to Mth 1, Mth 2, Mth 3]	NS
							Pain on first day of menstruation, Visual Analogue Score [BL to Mth 1, Mth 2, Mth 3]	**Reduced pain** Mth 1: -2.7 ($p=0.03$) Mth 2: -2.8 ($p=0.04$) Mth 3: -3.2 ($p=0.01$)
							Conventional analgesic medication use [BL to Mth 3]	**Reduced analgesic medication use**
Ee, et al (2016) [Australia, WPRO] [21]	Randomized controlled trial	Menopause, hot flushes (women, >40 years)	Standardized needle acupuncture to treat kidney yin deficiency.	8 weeks (10 treatments; 2 per week for 2 weeks, then weekly)	Non-insertive sham acupuncture	327 (163/ 164)	Hot flush score (mean) [BL to Wk 8]	NS
							Hospital Anxiety and Depression Scale [BL to Wk 8]	NS
							Quality of life (MENQoL) [BL to Wk 8]	NS

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Newton, et al. (2006) [USA, AMRO] [22]	Randomized controlled trial	Menopausal hot flushes	(1) *Actaea racemosa* (160mg/day) plus diet counselling (1 phone call; fruit and vegetable booklet (2) Multibotanical: *Actaea racemosa* (200mg/day), *Medicago sativa* (400mg), boron (4mg), *Vitex agnus-castus* (200mg), *Angelica sinensis* (400mg), *Chamaelirium luteum* (200mg), *Glycyrrhiza glabra* (200mg), *Avena sativa* (400mg), *Punica gratum* (400mg), *Eleuthrococcus senticosus* (stand. 0.8% eleuthrosides E and B; 400mg) plus diet counselling (1 phone call; fruit and vegetable booklet). (3) Multibotanical plus soy diet counselling – 5 phone calls from a clinical dietician and a 34-page booklet recommending 2 soy food servings/day (equiv. 12-20g soy protein) (4) Conjugated equine estrogen 0.625mg; + medroxy-progesterone acetate (2.5mg) for women with a uterus plus diet counselling (1 phone call; fruit and vegetable booklet).	12 months	Lactose capsules plus dietary counselling (1 phone call from a clinical dietician and a 34-page booklet reinforcing fruit and vegetable intake).	N=351 (257/77) 1: n=77 2: n=74 3: n=77 4: n=29	Frequency of vasomotor symptoms [BL to Mth 3, 6, 12]	Group 1, 2 & 3: NS Group 4: Mth 3 -4.55 ($p<0.001$) Mth 6 -3.86 ($p<0.001$) Mth 12 -3.76 ($p<0.001$) Overall, -4.06 ($p<0.001$)
							Intensity of vasomotor symptoms [BL to Mth 3, 6, 12]	Group 1, 2, 3 & 4: NS
							Wiklund Menopause Symptom Scale score [BL to Mth 3, 6, 12]	Group 1, 2 & 3: NS Group 4: Mth 3 -2.60 ($p<0.001$) Mth 6 -1.78 ($p<0.001$) Mth 12 -1.77 ($p<0.001$) Overall, -2.05 ($p<0.001$)

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
Ratnakumari, et al. (2018) [India, SEARO] [28]	Randomized controlled trial	Polycystic ovarian syndrome	Complex intervention comprising: (a) Cold abdominal mud pack (b) Cold water enema (c) Cold hip bath; (d) Hot foot immersion bath; (e) Partial massage to abdomen; (f) Partial massage to back; (g) Dietary changes: Fasting using fruit and vegetable juices and fluids; (h) Dietary changes: Raw vegetables, fruits, sprouts, vegetable soup for breakfast, and short vegetarian lunch meal; (i) Dietary changes: Boiled vegetables, steamed food; (j) yogic practice: *Asanas [supine: uttanapadasana, pawanmuktasana, naukasana, setu bandhasana; prone: bhujangasana, dhanurasana; sitting: vakrasana, baddha konasana; standing: katichakrasana, ardhakatichakrasana, dwikonasana, padahastasana], Pranayama [bhramari pranayama, surya bhedana pranayama, nadi shodhana pranayama], Kriya [kapalhati], Mudra [yoni mudra], Relaxation [savasana]*	12 weeks: (a) 10 mins, 6 days/wk; (b) once in 4 wks; (c) 15 mins, 6 days/wk; (d) 10 mins, twice in one week; (e) 10 mins, 3 days/wk; (f) 10 mins, 3 days/wk; (g) initial 3 days/ month; (h) next 18 days/ month; (i) final 7 days/ month; (j) 20mins, 6 days/wk excluding menstruation days	Waitlist	50 (25/25)	Ovarian volume [BL to Wk 12]	**Increased ovarian volume (left)** Right: NS Left: Intervention +3.68 Control -0.79 Between group p=0.032
							Ovarian size (cm) [BL to Wk 12]	Right: NS Left: NS
							Follicles antrum [BL to Wk 12]	**Increased follicle antrum (right)** Right: Intervention +5; Control -4 Between group p<0.001 Left: NS
							Largest follicle size (cm) [BL to Wk 12]	**Reduced follicle length** Right, Length: Intervention -0.1; Control +0.15 Between group p=0.016 Right, Width: NS Left, Length & Width: NS
							Total ovarian assessment (instrument not specified) [BL to Wk 12]	**Increased ovarian** Intervention: +6; Control: -3.5 Between group: p<0.001
							Body weight (kg) [BL to Wk 12]	**Increased body weight** Intervention: +6; Control: +0.0 Between group: p<0.001
							Body mass index (BMI) (kg/m^2) [BL to Wk 12]	**Increased BMI** Intervention: +2.36; Control: 0.0 Between group: p<0.001
							Chest circumference (cm) [BL to Wk 12]	**Increased chest circumference** Intervention: +4.25; Control: +0.75 Between group: p<0.001

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Waist circumference (cm) [BL to Wk 12]	**Increased waist circumference** Intervention: +5; Control: -1.25 Between group: p<0.001
							Hip circumference (cm) [BL to Wk 12]	**Increased hip circumference** Intervention: +6.75; Control: -0.25 Between group: p<0.001
							Mid-arm circumference (cm) [BL to Wk 12]	**Increased mid-arm circumference** Intervention: +3; Control: +0.0 Between group: p<0.001
							Waist-hip ratio [BL to Wk 12]	NS
							Cycle length [days] [BL to Wk 12]	Last menstrual period and first cycle: NS First and second cycle: NS Second and third cycle: NS
Shetty, et al. (2018) [India, SEARO] [26]	Randomized controlled trial	Primary dysmenorrhea (age 17-23 years old)	Needle stimulation of 12 acupuncture points. *Single needle stim.:* CV-4, CV-6. *Bilateral needle stim.:* KI-3, SP-8, ST-25, ST-29, ST-30, ST-36, BL-62, HT-7, LI-4, PC-6. *Needles:* 0.2 x 30mm. *Stimulation:* undisturbed. (*Duration*: 20 minutes. *Sessions*: 45 [1 per day; 15 per 30 days]. *Treatment initiation:* 6th day of menstrual cycle [not performed during menstruation])	90 days	Usual care	60 (30/30)	Pain intensity [10-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced pain** Dy 30: Acupuncture -2.86 Control -0.39 Between group, p<0.05 Dy 60: Acupuncture -4.75 Control -0.34 Between group, p<0.05 Dy 90: Acupuncture -4.76 Control +0.05 Between group, p<0.05

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Muscle/menstrual cramping [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced cramping** Dy 30: Acupuncture -1.20 Control +0.10 Between group, p<0.05 Dy 60: Acupuncture 1.43 Control +0.17 Between group, p<0.05 Dy 90: Acupuncture -1.60 Control +0.10 Between group, p<0.05
							Headache [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced headache** Dy 30 & 60: NS Dy 90: Acupuncture -0.30 Control -0.03 Between group, p<0.05
							Dizziness [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced dizziness** Dy 30: Acupuncture -0.84 Control -0.10 Between group p<0.05 Dy 60: Acupuncture -1.00 Control +0.03 Between group p<0.05 Dy 90: Acupuncture -1.00 Control +0.06 Between group p<0.05
							Diarrhea [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced diarrhea** Dy 30: Acupuncture -0.46 Control +0.20 Between group p<0.05 Dy 60: Acupuncture -0.53 Control +0.07 Between group p<0.05 Dy 90: Acupuncture -0.56 Control +0.20 Between group p<0.05

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Faint [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced faint** Dy 30: Acupuncture -0.40 Control -0.03 Between group p<0.05 Dy 60: Acupuncture -0.40 Control -0.16 Between group p<0.05 Dy 90: Acupuncture -0.43 Control +0.10 Between group p<0.05
							Mood changes [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced negative mood** Dy 30: Acupuncture -1.00 Control -0.04 Between group p<0.05 Dy 60: Acupuncture -0.90 Control -0.17 Between group p<0.05 Dy 90: Acupuncture -0.97 Control -0.10 Between group p<0.05
							Tiredness [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced tiredness** Dy 30: Acupuncture -1.00 Control -0.04 Between group p<0.05 Dy 60: Acupuncture -1.27 Control -0.04 Between group p<0.05 Dy 90: Acupuncture -1.27 Control -0.24 Between group, p<0.05
							Nausea [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced nausea** Dy 30: Acupuncture -0.70; Control -0.07 Between group p<0.05 Dy 60: Acupuncture -0.73 Control +0.13 Between group p<0.05 Dy 90: Acupuncture -0.87 Control +0.16 Between group, p<0.05

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Vomiting [4-point numerical rating scale] [BL to Dy 30, 60, 90]	**Reduced vomiting** Dy 30: Acupuncture -0.47 Control +0.03 Between group p<0.05 Dy 60: Acupuncture -0.47 Control +0.07 Between group p<0.05 Dy 90: Acupuncture -0.47 Control -0.00 Between group, p<0.05
Steels, et al. (2017) [Australia, WPRO] [24]	Randomized controlled trial	Menopausal symptoms	*Capsule: Trigonella foenum-graecum* L. de-husked seed extract (Libifem®), 300mg extract equiv. 9.9g dry herb, standardized for a minimum of 50% conent of forustanol saponins. Dose: 1 capsule twice daily, equivalent 600mg/day extract; with food at breakfast and evening meal	12 weeks	Placebo: Maltodextrin in identical capsule	104 (54/50)	Vasomotor symptoms (Menopause-Specific Quality of Life Questionnaire – MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced vasomotor symptoms** Herbal: Wk 4, -1.3; Wk 8, -1.7. Wk 12, -2.1 Placebo: Wk 4, +0.3; Wk 8, +0.2; Wk 12, +0.2 Between group, p<0.001
							Psychosocial symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced psychosocial symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.1; Wk 12, -1.0 Placebo: Wk 4, +0.1; Wk 8, -0.1; Wk 12, -0.1 Between group, p<0.001
							Physical symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced physical symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.0; Wk 12, -1.0 Placebo: Wk 4, -0.2; Wk 8, -0.4; Wk 12, -0.3 Between group, p<0.001

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Sexual symptoms (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced sexual symptoms** Herbal: Wk 4, -0.8; Wk 8, -1.4; Wk 12, -1.4 Placebo: Wk 4, +0.1; Wk 8, -0.3; Wk 12, -0.2 Between group, p<0.001
							Impact on Total Quality of Life (MENQOL) [BL to Wk4, Wk 8, Wk 12]	**Reduced impact on quality of life** Herbal: Wk 4, -3.5; Wk 8, -5.2; Wk 12, -5.4 Placebo: Wk 4, -0.3; Wk 8, -0.6; Wk 12, -0.4 Between group, p<0.001
Steels, et al. (2018) [Australia, WPRO] [23]	Randomized controlled trial	Menopausal hot flushes	Capsule: *Tinospora cardifolia* (stem), 100mg; *Asparagus racemosus* (root), 100mg; *Withania somnifera* (root), 100mg; *Commiphora mukul* (gum exudate), 225g. Dose: 1 capsule twice daily with breakfast and evening meal.	12 weeks	Placebo: Maltodextrin in identical capsule	104 (54/50)	Vasomotor symptoms [Menopause-Specific Quality of Life Questionnaire – MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced vasomotor symptoms** Herbal: Wk 4, -1.4; Wk 8, -1.9; Wk 12, -1.6 Placebo: Wk 4, +0.3; Wk 8, +0.2; Wk 12, +0.2 Between group, p<0.001
							Psychosocial symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced psychosocial symptoms** Herbal: Wk 4, -0.9; Wk 8, -1.1; Wk 12, -0.9 Placebo: Wk 4, +0.3; Wk 8, -0.1; Wk 12, -0.1 Between group, p<0.001

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							Physical symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced physical symptoms** Herbal: Wk 4, -0.8; Wk 8, -1.2; Wk 12, -0.9 Placebo: Wk 4, -0.2; Wk 8, -0.4; Wk 12, -0.3 Between group, p=0.002
							Sexual symptoms [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced sexual symptoms** Herbal: Wk 4, -0.7; Wk 8, -1.0; Wk 12, -1.3 Placebo: Wk 4, +0.1; Wk 8, -0.3; Wk 12, -0.2 Between group, p<0.001
							Impact on Total Quality of Life [MENQOL] [BL to Wk4, Wk 8, Wk 12]	**Reduced impact on quality of life** Herbal: Wk 4, -3.8; Wk 8, -5.2; Wk 12, -4.8 Placebo: Wk 4, +0.3; Wk 8, -0.6; Wk 12, -0.4 Between group, p<0.001
							7-day incidence of daytime hot flushes [BL to Wk4, Wk 8, Wk 12]	**Reduced incidence of hot flushes** Herbal: Wk 4, -8 (-30%); Wk 8, -14 (-50%); Wk 12, -18 (-64%) Placebo: Wk 4, -1 (-6%); Wk 8, -0.0 (0%); Wk 12, +4 (+22%) Between group, p<0.001

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
							7-day incidence of night sweats [BL to Wk4, Wk 8, Wk 12]	**Reduced incidence of night sweats** Herbal: Wk 4, -7 (-50%); Wk 8, -7 (-50%); Wk 12, -10 (-71%) Placebo: Wk 4, -4 (-36%); Wk 8, -3 (-27%); Wk 12, -1 (-9%) Between group, p<0.001
							7-day incidence of total flushes [BL to Wk4, Wk 8, Wk 12]	**Reduced incidence of total flushes** Herbal: Wk 4, -18 (-43%); Wk 8, -22 (-52%); Wk 12, -28 (-67%) Placebo: Wk 4, -17 (-19%); Wk 8, -17 (-19%); Wk 12, +1 (+3%) Between group, p<0.001
							Safety measurements – Blood pressure, weight (kg), fasting blood glucose, serum cholesterol, red cell count, hematocrit, mean cell volume, mean cell hemoglobin, total protein, albumin [BL to Wk4, Wk 8, Wk 12]	NS
Taylor, et al. (2018) [Australia, WPRO] [31]	Case report	Interstitial Cystitis	Naturopathic care including liquid herbal formula containing *Hypericum perforatum, Eleutherococcus senticosus, Scutellaria lateriflora, Schisandra chinensis, Crocus sativus,* (7.5ml BD), herbal tablet containing *Boswellia serrata, Curcuma longa, Apium*	2 weeks	Nil	1	Client self-reported symptom reduction	Increased energy and vitality, marked reduction in frequency and urgency of urinary symptoms, improved sleep onset and quality, reduction in edema in feet and ankles.

Author (Year) [Country, World Region]	Design	Study Population	Intervention	Dose/ Duration of Treatment	Control or Comparison group	No. Participants (Intervention/ Control)	Measure of Outcome	Outcome
			graveolens, Zingiber officinale, (2 tables BD); lifestyle counseling including sleep hygiene, stress reduction techniques; dietary advice including increased water consumption and reduction of aggravating foods.					
Watson, et al. (2014) [Australia, WPRO] [30]	Randomized controlled trial	Candidiasis	Tablet: Garlic powder, 350mg (allicin: 3200mcg)	14 days; 3 tablets twice daily	Placebo: tablets containing lactose, povidone, maize starch, talc, magnesium stearate	59 (29/30)	Proportion of 'cases' (women with colony counts of candida >100 CFU/ml in any given day during the last 7 days before menstruation) [BL to Wk4, Wk 8, Wk 12]	NS
							Vaginal quantitative counts (daily swabs for 2 weeks prior to menstruation) [BL to Wk4, Wk 8, Wk 12]	NS
							Vaginal itch (moderate to severe, compared to mild) [BL to Wk4, Wk 8, Wk 12]	NS
							Abnormal discharge (yes/no) [BL to Wk4, Wk 8, Wk 12]	NS
							Self-reported change in experienced symptoms of vaginitis (same, better, or worse than usual) [BL to Wk4, Wk 8, Wk 12]	NS

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27 Other Conditions

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HIGHLIGHTS

- Naturopaths/naturopathic doctors treat diverse health conditions through all stages of life.
- While patients seeking naturopathic care primarily present with chronic conditions, naturopaths/NDs also provide acute care as well as preventive and palliative care.
- Research suggests that naturopathic care may be beneficial in the treatment of obesity, respiratory and genitourinary conditions.
- Further research investigating the role of naturopathic care in acute conditions is warranted.
- 85.7% of clinical studies investigating naturopathic treatment for other conditions report a positive outcome in at least one primary or secondary outcome measure.

Primary health care presents health professionals with diverse populations experiencing diverse health conditions ranging from chronic, lifestyle-related health concerns such as overweight and obesity, everyday illnesses such as colds and flu, and non-life-threatening conditions which have significant impact on an individual's quality of life such as urinary incontinence and sexual dysfunction. In line with their training as primary care practitioners, naturopaths/naturopathic doctors (NDs) provide care to the patients through all stages of life including preventive, acute, chronic and palliative care.

Overview of Studies

This chapter is dedicated to highlighting the original clinical research (n=14) conducted by naturopathic clinicians on conditions not presented elsewhere in this section. This research includes a total of 510 participants and was conducted in India (n=6), the United States of America (USA) (n=4), Germany (n=1), Australia (n=1), Canada (n=1), and Puerto Rico (n=1). The study designs include randomized control trials (n=7), case reports (n=5), and uncontrolled trials (n=2). There was a range of interventions investigated in these studies including yoga (n=5), applied nutrition (n=3), herbal medicine (n=2), acupuncture (n=2), clinical nutrition (n=2), homeopathy (n=1), hydrotherapy (n=1), bodywork (n=1), and mindfulness meditation (n=1). One study combined more than two types of treatment within a complex naturopathic intervention. The conditions examined in the studies include overweight and/or obesity (n=6), respiratory conditions (n=6), and genitourinary conditions (n=2). Of all the naturopathic clinical studies examining populations with other health conditions, 85.7% reported a positive outcome in at least one primary or secondary outcome measure. Details of the studies are available in *Table 27.1: Clinical research investigating other conditions conducted by naturopathic researchers.*

Implications

There is emerging evidence across a range of conditions to suggest that naturopathic interventions may be beneficial for patients with overweight and obesity, respiratory conditions and genitourinary conditions. While some research is based on case reports, there is a substantial and growing body of evidence from clinical trials using standardized measures that report favorable outcomes.

Naturopaths/naturopathic doctors treat diverse health conditions through all stages of life. While patients primarily present with chronic health conditions, naturopaths/naturopathic doctors also provide care to patients during acute phases of illness as well as providing preventive and palliative care [1]. The wellness orientation of naturopaths/naturopathic doctors and the focus on lifestyle and preventive behaviours supports their ability to provide care to patients irrespective of their health condition; in some instances, with the aim to resolving the condition, while in others reducing symptoms and improving quality of life. The holistic approach to healthcare and the inter-systems approach to treatment facilitated by naturopathy's philosophical

and principles-based approach to care supports patients with multiple morbidities or pathologies, which is seldom captured by research studies.

The breadth of treatments employed by naturopaths/naturopathic doctors combined with the variability in each patient's health needs and the imperatives of the naturopathic philosophies and principles to deliver individualized patient care results in different treatments approaches being considered for the same condition. Such variations in treatment can be seen within the practices of individual naturopaths/naturopathic doctors as well as between naturopathic clinicians, also likely to be the result of the patient-centered and individualized focus of naturopathic practice. Additional research is required to fully understand the effectiveness of the range of naturopathic treatments across different symptoms and conditions.

Studies based on specific conditions:

Overweight or obesity

Treatments for overweight or obesity are examined in six clinical studies, two conducted in the USA [2, 3], three in India [4-6] and one in Germany [7]. The study interventions include yoga (n=2) [6, 7], applied nutrition (n=3) [2, 5, 6] clinical nutrition (n=1) [3] and a complex intervention (n=1) [4]. A randomized, controlled trial conducted in Germany examined the impact of a yoga intervention on a range of self-reported and anthropometric outcomes among females with abdominal obesity, compared to a waitlist control group [7]. The women participated in a 12-week intervention involving a full day yoga workshop at the beginning of the study followed by 90-minute yoga classes twice weekly. Compared to the control group, participants in the yoga group reported an improved quality of life (Short Form-23: -3.8; p=0.001), self-esteem (Rosenberg's Self Esteem Scale: -0.02; p=0.03), body awareness (Body Awareness Questionnaire: +9.3; p=0.001) and trust in their bodily sensation (Body Responsiveness Scale: +4.4; p<0.001) at the end of the study period. Favorable improvements from baseline were also recorded for anthropometric measurements in the yoga group, compared to control, including waist circumference (-3.7cm; p=0.001), waist-hip ratio (-0.02; p=0.03), body weight (-2.4kg; p=0.003), body mass index (-0.8 kg/m2; p=0.008), body fat (-1.7%; p=0.01) and muscle mass (+0.8%; p=0.01).

A randomized controlled trial conducted in India employed lemon juice containing lemon seeds combined with a calorie-restricted diet, compared with lemon juice without seeds and the same diet, for individuals with obesity (n=30) [5]. By the end of the study period (7 days), participants in the group consuming lemon juice with lemon seeds had a greater reduction in body mass index (-2.0 vs -1.4 kg/m2; p=0.0001), weight (-4.9 vs -3.3 kg; p=0.004), waist circumference (-11.3 vs -3.4; p=0.004), and hip circumference (-3.5 vs -2.9; p=0.004) but no difference in change to waist-hip ratio.

Clinical finding

Yoga practice may improve quality of life, self-esteem, body awareness, trust in bodily sensation, waist circumference, waist-hip ratio, body weight, body mass index, body fat and muscle mass in women with abdominal obesity.

An uncontrolled study conducted in India involving 47 patients with obesity examined the impact of a low fat, high fiber, vegetarian diet along with daily yoga practice [6]. The study lasted for 6 days and resulted in a reduction of BMI -0.57 (p<0.01), a reduction in waist circumference -1.69 (p<0.01), reduction in hip circumference -1.69 (p<0.01), reduced HDL -2.88 <p<0.01) a reduction in leptin -23.75 (p<0.01), an increase in hand grip strength and postural stability.

Respiratory Conditions

Six clinical studies have examined naturopathic treatments for respiratory conditions including pulmonary tuberculosis [8], asthma [9-11], chronic rhinosinusitis [12], and recurrent symptoms related to the common cold [13]. The studies were in India (n=2) [8, 12], USA (n=2) [10, 11], Australia (n=1) [13], and Puerto Rico (n=1) [9]. A review of 21 patients with asthma from a clinic in Puerto Rico revealed that 94% of patients <21 years of age and 86% of patients >21 years of age experienced improvement in their asthma symptoms [9]. The treatment intervention included bromelain 250 mg TID, an herbal product individualized for each patient, a cough elixir 10 or 30 gtt QID and an individualized homeopathic remedy.

Clinical finding

Yoga combined with breath awareness may improve sputum microscopy and postero-anterior chest x-ray results in individuals with pulmonary tuberculosis.

Naturopathic treatment of pulmonary tuberculosis was examined through a randomized controlled trial conducted in India. The study compared a yoga intervention in a naturopathic setting with breath awareness over

60 days among 48 individuals with confirmed pulmonary tuberculosis [8]. A greater proportion of participants in the yoga group had improved sputum microscopy at day 30 (19/25 vs 10/23; p=0.045), day 45 (24/25 vs 12/23; p=0.002), and day 60 (10/13 vs 4/19; p=0.005) compared to the breath awareness group. Similarly, more of the yoga group than the breath awareness group had an improved postero-anterior chest x-ray at the end of the study period (19/25 vs 3/22; p=0.001).

Clinical finding

High-lactoferrin and immunoglobulin whey protein may reduce the total occurrence of the common cold and cold-associated symptoms in individuals with frequent symptoms related to the common cold.

A randomized controlled trial (n=60) conducted in a naturopathic hospital in India examining the effects of a 10-day acupuncture intervention compared with a steam inhalation intervention for individuals with chronic rhinosinusitis [12]. The acupuncture group received a standardized acupuncture treatment for 20 minutes per day while the steam inhalation group underwent a daily 20-minute protocol involving cycles of steam inhalation. Both groups reported a statistically significant change in symptoms. However, the acupuncture group had a greater reduction in symptom frequency (-1.20 vs -1.03) but a lesser reduction in Sino-Nasal Outcome Test scores (-3.47 vs -4.83). An 90-day placebo-controlled randomized trial conducted in Australia investigated the effects of high-lactoferrin and immunoglobulin whey protein in individuals with frequent symptoms related to the common cold (n=105) [13]. Although no differences in cold duration or severity were reported between groups, the lactoferrin group reported a lower number of total occurrences of the common cold at Day 45 (0.67 vs 1.40; p<0.001) and Day 90 (0.93 vs 2.26; p<0.001). They also had a lower number of cold-associated symptoms compared to placebo (208 vs 288; p<0.05).

Genitourinary Conditions

Two clinical studies investigated genitourinary conditions: one examining acupuncture treatment for sexual dysfunction (n=1) [14]; and a case report describing treatment of urinary incontinence conducted in India (n=1) [15]. The former, an uncontrolled trial conducted in Canada, used acupuncture alongside antidepressant medications to treat individuals with secondary sexual dysfunction (n=35) [14]. The acupuncture was administered in a naturopathic setting weekly for 12 weeks, and participants were followed for an additional 4 weeks to measure any sustained effects after treatment ceased. The study found participants had reduced anxiety (-2.8; p=0.01) but reported no change to depression scores. Participants also reported improved total Sexual Function Visual Analogue Scale of +62.28 (p=0.01), as well as significant increases in all domains (desire/libido, erection, ejaculation delay, orgasm delay, frequency of sex). In addition to the improvement in function, participants also reported improved sexual experience (Arizona Sexual Experience Questionnaire: -1.59; p=0.027).

Table 27.1 Original research on other conditions conducted by naturopathic researchers

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Cramer, et al. (2016) [Germany, EURO] [7]	Randomized controlled trial	Obesity (females with abdominal obesity)	Traditional hatha yoga	12 weeks: full day workshop followed by 2 x weekly 90-minute classes of traditional hatha yoga	Wait list	60 (40/20)	Short form-23 [BL to Wk 12]	**Reduced impact on quality of life** Yoga: -3.7; Wait list: +0.01 Between group: -3.8 (p=0.001)
							Rosenberg Self Esteem Scale [BL to Wk 12]	**Reduced impact on self-esteem** Yoga: -0.02; Wait list: -0.0 Between group: -0.02 (p=0.03)
							Perceived Stress Scale [BL to Wk 12]	**Reduced stress** Yoga: -3.1; Wait list: -1.7 Between group: -3.1 (p=0.016)
							Body Awareness Questionnaire [BL to Wk 12]	**Increased body awareness** Yoga: +6.1; Wait list: -1.0 Between group: +9.3 (p=0.001)
							Body Responsiveness Scale [BL to Wk 12]	**Increased body responsiveness** Trust in bodily sensations Yoga: +3.5; Wait list: -0.5 Between group: +4.4 (p<0.001)
							Waist circumference (cm) [BL to Wk 12]	**Reduced waist circumference** Yoga: -3.7; Wait list: +.01 Between group: -3.8 (p=0.001)
							Waist-hip ratio [BL to Wk 12]	**Reduced waist-hip ratio** Yoga: -0.02; Wait list: -0.0 Between group: -0.02 (p=0.03)
							Body weight (kg) [BL to Wk 12]	**Reduced body weight** Yoga: -1.5; Wait list: +0.7 Between group: -2.4 (p=0.003)
							Body mass index [BL to Wk 12]	**Reduced BMI** Yoga: -0.5; Wait list: +0.3 Between group: -0.8 (p=0.008)
							Percentage of body fat (%) [BL to Wk 12]	**Reduced body fat** Yoga: -1.4; Wait list: -0.1 Between group: -1.7 (p=0.01)

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							Percentage of body muscle mass (%) [BL to Wk 12]	**Increased muscle mass** Yoga: +0.6; Wait list: -0.0 Between group: +0.8 (p=0.01)
							Blood pressure (mmHg) [BL to Wk 12]	NS
Frances (1998) [USA, AMRO] [11]	Case reports	Asthma (adults)	Concomitant therapeutics highly variable but included: *Passiflora incarnata* tincture, *Piper methysticum* tincture, *Verbascum thapsus* spp tincture, *Eriodictyon* spp tincture, *Aspidosperma quebracho* tincture, *Oplopanax horridus* tincture, *Eleutherococcus senticosus* tincture, *Glycyrrhiza glabra* glycerite, *Echinacea* spp tablets, *Astragalus propinquus* tincture, *Eupatorium perfoliatum* tincture, B complex, antioxidants, homeopathic remedies, *Chelidonium majus* tincture, *Taraxacum officinale* tincture, *Silybum marianum* tincture, *Cynara scolymus* tincture, *Bupleurum falcatum* tincture, *Berberis* spp tincture, *Althaea officinalis* tincture, *Foeniculum vulgare* tincture, *Hypericum perforatum* tincture, *Actaea racemosa* tincture, *Panax ginseng* tincture, *Trifolium pratense* tincture	Weeks to years	Nil	6	Beta-agonist inhaler use	**Elimination or substantial reduction in use**

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Jisha Mol, et al. (2017) [India, SEARO] [12]	Randomized controlled trial	Rhinosinusitis (chronic)	Acupuncture (bilateral LI4, LI20, ST2 and ST36; unilateral EX-1 and GV23): 20 minutes daily	10 days Group 1: 20 minutes; 4 cycles of steam (3 minutes) and withdraw (1 – 2 minutes) Group 2: 20 minutes daily	Steam inhalation: 20 minutes daily; 4 cycles of steam (3 minutes) and withdraw (1 – 2 minutes)	60 (30/30)	Sino-Nasal Outcome Test [BL to Dy 10]	**Reduced symptoms** Inhalation: -4.83 (p=0.05) Acupuncture: -3.47 (p=0.005)
							Symptom frequency [BL to Dy 10]	**Reduced frequency** Inhalation: -1.03 (p=0.05) Acupuncture: -1.20 (p=0.001)
Khamba, et al. (2013) [Canada, AMRO] [14]	Uncontrolled trial	Secondary sexual dysfunction (adults)	Acupuncture (Kd3, GV4, UB23, Ht7, PC6). Intervention delivered as protocol for Heart *Yin* Deficiency and Kidney *Qi* Deficiency. Adjunctive to antidepressant medication (SSRIs and SNRIs)	12 weeks (+ 4 week follow up) – intervention administered weekly	Nil	35	Beck Anxiety Inventory (BAI)	**Reduced anxiety** -2.8 (p=0.01)
							Beck Depression Inventory, Second Edition (BDI-II)	NS
							The Sexual Function Visual Analogue Scale (SFVAS)	**Increased sexual function** Total: +62.28 (p=0.01) Desire/Libido: +13.9 (p=0.030) Erection: +12.0 (p=0.012) Ejaculation delay: +19.2 (p=0.03) Orgasm delay: +17.0 (p=0.025) Frequency of sex: +12.4 (p=0.04)
							The Arizona Sexual Experience Questionnaire (ASEX)	**Reduced impact on sexual experience** Total: -1.59 (p=0.027) Drive: -0.6 (p=0.014) Arousal: NS Erection: -0.5 (p=0.015) Ability to reach orgasm: -0.5 (p=0.027) Satisfaction from orgasm: NS
Neuendorf, et al. (2019) [USA, AMRO] [2]	Randomized controlled trial	Overweight/ obese (adults)	Elimination of foods in response to IgG test result	12 weeks	Waitlist	30 (20/10)	Serum IgG titres	NS

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Rodriguez Malavé (1991) [Puerto Rico, AMRO] [9]	Case reports	Asthma	Bromelain (>20 year only): Ma huang compound (>20 year only): extracts of *Ephedra sinica* 200 mg (standardized to 12 mg ephedrine), *Zingiber officinale* 65 mg, *Glycyrrhiza glabra* 50 mg (standardized to 5% glycyrrhizic acid), *Althaea officinalis* 50 mg (standardized to mucilage content of 30 – 40%) 50 mg, *Drosera rotundifolia* 40 mg, *Euphorbia hirta* 40 mg, *Polygala senega* 40 mg, *Hydrastis canadensis* 20 mg (standardized to 5% total alkaloids; Compound herbal cough elixir (<21 yr only): *Glycyrrhiza glabra* root, *Inula helenium* root, *Trifolium pratense* flower, *Prunus serotina* bark, *Marrubium vulgare* aerial parts, *Grindelia robusta* aerial parts, *Lobelia inflata* leaf and seed, *Foeniculum vulgare* fruit, *Lomatium dissectum* root, *Pinus strobus* bark, *Populus* spp. bud; Constitutional homeopathic remedy	Bromelain: 250mg three times daily Herbal product: 1 tablet four times daily Cough elixir: 10 or 30 drops four times daily Homeopathic remedy: individualised	Nil	21 yrs (1) 51 yrs (2) 27 yrs (3) underage (4) 21 yrs (5) 24 yrs (6)	Number of subjects improved (compared to baseline)	**Greater number of improved subjects** <21 yr: 16/17 (94%) >20 yr: 25/29 (86.2%)

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Shetty and Mooventhan (2015) [India, SEARO] [4]	Case report	Obesity	Initial 15-day admission: yoga sessions (60 mins day), naturopathic treatment (90 – 120 minutes per day) involving hydrotherapy, diet and fasting, mud therapy and massage therapy. Following 2 years of self-care patient was admitted for 10 days every 2 years (2010, 2012, 2014).	15 days (+10 days every 2 years for 6 years)	None	1	Body weight (kg) (BL to Dy 15, Yr 2, Yr 6)	**Reduced body weight** Dy 15: -6.1; Yr 2: Weight maintained; Yr 6: -22.7 (101 kg to 94.9 kg)
							Body mass index (BMI) (kg/m^2) [BL to Dy 15, Yr 2, Yr 6]	**Reduced BMI** Dy 15: -2.35; Yr 2: Changed from Class-II Obesity to Class-I Obesity; Yr 6: Changed to Overweight or Pre-obese (-8.61)
Sowmya (2018) [India, SEARO] [5]	Randomized controlled trial	Obesity	Group 1: Lemon juice with lemon seeds and calorie restricted diet	7 days	Group 2: Lemon juice alone with calorie restricted diet	30 (15/15)	C-Reactive Protein (mg/dL) [BL to Dy 7]	NS
							Body mass index (kg/m^2) [BL to Dy 7]	**Reduced BMI** Lemon seeds: -2.0; Lemon juice only: -1.4 Between group: p=0.0001
							Weight (kg) [BL to Dy 7]	**Reduced body weight** Lemon seeds: -4.9; Lemon juice only: -3.3 Between group: p=0.0001
							Waist circumference (cm) [BL to Dy 7]	**Reduced waist circumference** Lemon seeds: -11.3; Lemon juice only: -3.4 Between group: p=0.004
							Hip circumference (cm) [BL to Dy 7]	**Reduced hip circumference** Lemon seeds: -3.5; Lemon juice only: -2.9 Between group: p=0.004
							Waist-hip ratio [BL to Dy 7]	NS
Telles, et al (2009) [India, SEARO] [6]	Uncontrolled trial	Obesity	Low fat, high fiber, vegetarian diet and 5 hours of daily yoga practice	6 days	Nil	47	Body mass index (kg/m^2) [BL to Dy 6]	**Reduced BMI** -0.57 ($p<0.01$)
							Waist circumference (cm) [BL to Dy 6]	**Reduced waist circumference** -1.72 ($p<0.01$)
							Hip circumference (cm) [BL to Dy 6]	**Reduced hip circumference** -1.69 ($p<0.01$)

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
							High density lipoprotein (HDL) cholesterol (mg/dl) [BL to Dy 6]	**Reduced HDL cholesterol** -2.88 ($p<0.01$)
							Fasting serum leptin (ng/ml) [BL to Dy 6]	**Reduced leptin** -23.75 ($p<0.01$)
							Total cholesterol (mg/dl) [BL to Dy 6]	NS
							Low-density lipoprotein (LDL) cholesterol (mg/dl) [BL to Dy 6]	NS
							Serum triglycerides (mg/dl) [BL to Dy 6]	NS
							Hand grip strength (kg) [BL to Dy 6]	**Increased hand grip strength** Right: +2.09 ($p<0.001$); Left: +2.00 ($p<0.01$)
							Postural stability (sec) [BL to Dy 6]	**Increased postural stability** At 20 sec: +11.03 ($p<0.001$) At 40 sec: +24.41 ($p<0.001$) At 60 sec: +33.91 ($p<0.001$)
Vinchurkar and Arankalle (2015) [India, SEARO] [15]	Case Report	Urinary incontinence	Yoga Asanas (postures) – *Uttanapadasana* (raised leg pose), *vipartiakaranai* (legs up the wall pose), *Naukasana* (boat pose) Yoga *pranayamas* (breathing) – *Nadi shodhana* (alternative nostril breathing), *Bhramari* (Humming bee breath) Yoga *bandhas* and *mudras* – *Moolabandha* (perineal lock), *Ashwini mudra* (anal lock) Yoga meditation – mindfulness meditation	21 days – twice daily practice: *uttanapadasana* (5 x 30 seconds with 2 – minute rest periods), *Vipartiakarani* (5 x 15 seconds with 2 minute rest periods), *Naukasana* (5 x 10 seconds with 2 minute rest	Nil	1	Resting heart rate (beats/min) [BL to Dy 21]	**Reduced resting heart rate** -2
							Blood pressure (mmHg) [BL to Dy 21]	**Reduced (systolic) blood pressure** Systolic: -6; Diastolic: -0.0
							Weight (kg) [BL to Dy 21]	**Reduced weight** -1.9
							Body mass index (kg/m^2)	**Reduced BMI** -0.7
							Frequency volume chart score	**Reduced frequency** -2
							International Consultation on Incontinence Modular Questionnaire – Urinary Incontinence Short Form	**Reduced incontinence** -7

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
				periods), *Nadi shodhana* (10 rounds), *Bhramari* (5 rounds), *Moolabandha* (10 – 15 rounds), *Ashwini mudra* (5 rounds), Meditation (10 min)				
Virdee, et al. (2015) [USA, AMRO] [10]	Case report	Asthma	Elimination diet informed by individualized results of enzyme-linked immunosorbent assay (ELISA) for IgG antibody assessment. Trial period of complete avoidance of potential allergens while monitoring for symptom changes	90 days	Nil	1	Medication [BL to Dy 90]	**Reduced medication use** Patient A Fluticasone-salmeterol: twice daily vs none Albuterol: twice daily vs occasional use in cold weather Patient B: Montelukast sodium: At bedtime vs none Fluticasone-salmeterol: Twice a day (Wk 19) vs occasionally Albuterol: Every night vs at least every night Cetirizine hydrochloride: daily vs none
							Asthma attack	**Reduced frequency** Patient B: 2 – 3 attacks per week vs one in first 21 days of treatment and then none
							Pulse Oxygen	Patient B: 86-95% vs 96%
							Physical exam	**Reduced wheezing** Patient B: audible wheezing vs clear lungs from 21 days
							Subjective asthma symptom severity	**Reduced severity** Patient A: 9/10 vs 0/10

Author (year) [Country, World region]	Design	Study Population	Intervention	Duration and dose	Control or Placebo	No. Participants (Intervention/ Placebo)	Measure of Outcome	Outcome
Viswesw-araiah and Telles (2004) [India, SEARO] [8]	Randomized controlled trial	Pulmonary tuberculosis	Yoga	60 days, 6 x 1 hr sessions per week	Breath awareness	48 (25/23)	Improved sputum microscopy [BL to Dy 30, Dy 45, Dy 60]	**Greater incidence of improved microscopy** Dy 30: Yoga, 19/25; Breath, 10/23 Between group, p=0.045 Dy 45: Yoga, 24/25; Breath, 12/23 Between group, p=0.002 Dy 60: Yoga, 10/13; Breath, 4/19 Between group, p=0.005
							Improved postero-anterior chest x-ray	**Greater incidence of improved chest x-ray** Yoga: 19/25; Breath: 3/22 Between group: p=0.001
Vitetta, et al. (2013) [Australia, WPRO] [13]	Randomized controlled trial	Cold- related symptoms (frequency)	Bovine lactoferrin (Lf) 400mg and whey protein Ig rich fraction (IgF) 200mg daily	90 days	Placebo	105 (53/52)	Total cold events [BL to Dy 45, Dy 90]	**Reduced cold events** **Dy 1 – 45:** Lactoferrin, 0.67; Placebo, 1.40 Between group, p<0.001 **Dy 46 – 90:** Lactoferrin, 0.38; Placebo, 1.02 Between group, p<0.001 **Dy 1 – 90:** Lactoferrin, 0.93; Placebo, 2.26 Between group: p<0.001
							Total number of cold associated symptoms [BL to Dy 90]	**Reduced symptoms** Lactoferrin: 208; Placebo: 288 Between group: p<0.05
							Cold duration [BL to Dy 90]	NS
							Cold severity [BL to Dy 90]	NS
Yazaki, et al. (2010) [USA, AMRO] [3]	Randomized controlled trial	Overweight	1000 mcg of chromium picolinate/day	6 months	Placebo	80 (40/40)	Body mass index [BL to Mth 6]	NS
							Fasting glucose (mg/dl)	NS
							Fasting serum insulin (u/ml)	NS
							Cholesterol (mg/dl)	NS
							High-sensitivity C-reactive protein (mg/dl)	NS

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28 Other Research Publications Related to Health Conditions

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HIGHLIGHTS

- Naturopathic researchers have published over 1,456 journal articles in indexed peer-reviewed journals related to health conditions.
- Observational studies have an important role in understanding the etiology, progression and management of health conditions.
- Naturopathic researchers have published over 363 observational studies in the last 30 years.
- Reviews and meta-analyses are an important avenue for researchers to synthesize existing evidence related to a specific health condition. As such, reviews and meta-analyses assist readers in having a more comprehensive understanding of the evidence-base, and support evidence-informed policy and practice as well as identifying gaps in the existing evidence to direct new research.
- Naturopathic researchers have published over 357 reviews and metanalysis related to health conditions in the last 30 years.

Naturopathic researchers have published over 1,456 journal articles in indexed peer-reviewed journals related to health conditions and roughly half of these are reviews and meta-analyses (n=357; 24.5%) or observational studies (n=363; 24.9%). These types of articles present an important contribution in the healthcare field to the understanding of health, illness, and its management. Information contained in these articles not only adds to naturopathic clinicians' knowledge, but these studies also provide important summaries and insights for other stakeholders including policymakers, educators, other healthcare practitioners and the patient community.

This chapter provides an overview of the topics covered in the reviews and meta-analyses and the observational studies related to health conditions that have been written by naturopathic researchers. Due to the substantial number of papers across these two categories of research publications, it is not possible to provide a comprehensive description of the studies produced by naturopathic researchers. Instead, this chapter also provides an indicative overview of the topic areas that may be covered by these articles, by presenting a more detailed description of the two most frequently discussed health conditions within each article type.

Observational studies

Observational studies have an important role in understanding the etiology, progression and management of health conditions. Through epidemiological research, observational studies can uncover potential risk factors and protective behaviors that influence disease onset or prognosis. Survey research is used to identify the health behaviors and health service use among patient populations with the condition of interest, or practice behaviors and clinical experience among clinicians treating patients for the condition. Qualitative research can also be used to describe the experience of patients living with the health condition.

Naturopathic researchers have conducted observational studies in USA (n=184), Australia (n=70), Canada (n=39), India (n=37), Germany (n=13), Saudi Arabia (n=8), the United Kingdom (n=4), New Zealand (n=3), Sub-Saharan Africa (n=3), South Africa (n=2), France (n=1), Japan (n=1), and Uganda (n=1). This research encompassed health conditions related to cancer (n=113), musculoskeletal health (n=55), mental health (n=52), neurological condition (n=43), women's health (n=44), urogenital conditions (n=24), cardiovascular health (n=21), infectious disease (n=17), endocrine conditions

(n=15), weight management (n=15), gastrointestinal conditions (n=13), wellness and preventive health (n=11), respiratory health (n=8), among other conditions (n=9).

The observational studies focused on cancer-related health conditions covered a broad range of sub-topics. One important topic area examined in these studies is cancer pathophysiology [1-3], symptom presentation [4-7] and etiology including genetic factors [2, 8-15] and the role of immunity in cancer care [16-20]. Naturopathic researchers are also conducting observational studies to understand treatments used by patients [21-44], and the Traditional and Complementary Medicine (T&CM) health providers they are accessing for their cancer care [21, 22, 27, 29, 34, 40, 41, 43-46]. Naturopathic researchers are also employing observational study designs to describe the treatments used by naturopaths/naturopathic doctors for the management of cancer-related conditions to inform future research and practice [47-52]. The naturopathic research in this area is also providing insights into the attitudes of individuals with cancer [22, 23, 38, 43, 53, 54] and health professionals [47, 48, 55] towards T&CM. In addition to understanding cancer pathophysiology and patterns of use, naturopathic researchers have also used observational research to collect safety data associated with pharmaceutical [25, 56, 57] and T&CM treatments [25, 33, 37, 42, 58] for cancer-related conditions.

Naturopathic researchers have employed observational study designs to explore musculoskeletal conditions such as osteoarthritis [59-61], neck pain [62-65], back pain [65, 66], and acute injuries [67-78]. The research covers a variety of topics related to musculoskeletal health conditions, including the associations between naturopathic interventions and musculoskeletal health [62, 79-82] and comorbidities and risk factors associated with musculoskeletal health conditions [4, 69, 70, 73, 74, 77, 83-99]. A notable number of studies also examined the economic implications of musculoskeletal conditions and their management [100-102], and provided innovative contributions to outcome evaluation which advance musculoskeletal clinical research methods [63, 72, 76, 78, 92, 103-105]. They have also explored the use of complementary medicines and other health services by individuals with musculoskeletal health conditions [60, 80, 106-108].

Reviews and Meta-Analyses

Reviews and meta-analyses are an important avenue for researchers to synthesize existing evidence related to a specific health condition. As such, reviews and meta-analyses assist readers in having a more comprehensive understanding of the evidence-base, and support evidence-informed policy and practice as well as identifying gaps in the existing evidence to direct new research. Naturopathic researchers have published reviews and meta-analyses in Australia (n=109), Canada (n=93), USA (n=86), Germany (n=57), India (n=10), Saudi Arabia (n=1) and New Zealand (n=1). These reviews and meta-analyses focused on numerous health conditions including mental health (n=81), cancer (n=67), musculoskeletal (n=51), gastrointestinal (n=39), women's health (n=39), neurological (n=25), cardiovascular (n=21), endocrine (n=17), infectious (n=12), respiratory (n=10), skin conditions (n=9), weight management (n=8), among other conditions (n=12).

Within the category of mental health conditions, naturopathic researchers have published reviews and meta-analyses commonly focused on depression [109-127], anxiety [117, 121, 124, 128-138], schizophrenia and psychosis [139-144], bipolar disorder [118, 145, 146], insomnia [147, 148], and other psychiatric conditions [149-151]. The majority of these articles explored naturopathic treatment options for mental health conditions, with attention given to herbal medicines [115, 117, 124, 128, 133, 138, 148, 152-163], clinical nutrition [109-111, 113, 118, 141, 144, 164-170], yoga [120, 127, 136, 139, 150, 151, 171-173], mind-body medicine [140, 171, 174], acupuncture[149], diet [114, 129, 142, 175] and lifestyle medicine [119, 122, 129, 135, 176-178]. Naturopathic researchers also conducted reviews examining the etiology and pathophysiology of mental health conditions, including environmental causes [179-181], the role of behaviors such as use of devices (e.g. smartphones) [135, 137, 178], and the importance of other physiological factors such as the microbiome [168-170, 175, 179, 181, 182]. Many of these reviews and meta-analyses targeted the mechanisms [109, 117, 161, 163, 165] or efficacy/effectiveness [109, 111, 112, 114, 115, 117, 120, 121, 123, 124, 126, 127, 129, 130, 132, 133, 136, 138-142, 146-151, 153, 155, 159, 161, 164-167, 171-174, 176, 178, 183-185] of these treatments for mental health conditions.

Naturopathic researchers have also published reviews and meta-analyses focused on specific cancer-related conditions (e.g. breast cancer [121, 172, 186-201], lung cancer [202-207], colorectal cancer [208-211]) as well as cancer more generally [188, 212-231]. These reviews encompass all points along the cancer journey including prevention [212, 213, 218, 225, 232], treatment [188, 189, 199, 201, 213, 217, 219, 222, 232-238], survivorship [191, 227] and palliative care [223, 228]. A broad range of treatments are investigated in these papers including herbal medicines [186-188, 193, 195, 202, 206, 207, 217, 222, 226, 229, 233, 235, 239, 240], clinical nutrition [189, 194, 203, 204, 208, 209, 213, 215, 219-221, 230, 232, 234, 241-243], mind-body medicine [200], acupuncture [223] and yoga [172, 191, 228]. As well as investigating the efficacy/effectiveness of these treatments, a number of studies also explored their pharmacokinetics [220, 224] and safety [188, 220, 233, 236, 241, 244]. Reviews also examined the

available evidence regarding the experiences of cancer patients [228, 231] and the role of health professionals in supporting cancer patients [196, 201, 214], particularly within the context of T&CM use.

Implications

Naturopathic researchers have produced a considerably volume of research to contribute to the wider understanding of the pathophysiology, treatment, and context of diverse health conditions. While the observational research and reviews/meta-analyses published by naturopathic researchers commonly focus on treatments used in naturopathic practice, it is also important to note that a substantial proportion of this research also examines the etiology and pathophysiology of health conditions from both a macro (e.g., environmental causes) and micro (e.g., genetic influences) viewpoint. Equally, naturopathic researchers are exploring both prevention and treatment, and in doing so, they ensure the naturopathic principle of *Prevention* is supported by the research they produce. The breadth of information reflected in the numerous papers published by naturopathic researchers assist in mapping the landscape of care provided to patients, translating existing knowledge into policy and practice, and opening new avenues for future research; all of which support better patient outcomes and health in the community.

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