White Paper

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April 20, 2016

Overview

The objective of this white paper is two fold: to provide an overview of chronic pain and inflammation, and to review the evidence supporting the efficacy, safety and tolerability of the proprietary preparation that includes boswellia, urtica dioica, equisetium arvensae, apium graveolens and allium sativum and vitamin B_1 (referred to as the 'blend') in the treatment of patients with chronic musculoskeletal pain. These five herbs have been demonstrated to have activity at several anti-inflammatory pathways as well as analgesic properties that are effective in treating chronic musculoskeletal pain.

INTRODUCTION

Chronic Pain

Chronic pain is a predominant manifestation of disease resulting in impaired mobility, emotional stress, loss of function and reduced quality of life. It is estimated that up to 12% of the adult population suffers from some form of chronic pain.[1] Chronic pain is frequently refractory to treatment and its prevalence continues to increase. Epidemiological studies report that up to 20% of those with chronic pain are refractory to standard, traditional therapies such as non-prescription analgesics or prescription COX-inhibitors and opioids.[2] It is estimated these conditions result in 60 billion dollars in lost productivity each year and will likely increase as individuals live longer and survive with more treatable medical conditions.[3]

The World Health Organization estimates that 50% of those with chronic pain report the source occurs in limbs and joints and 33% report the lower back as the source of pain.[4] Joint and back pain is most commonly caused by arthritic conditions and is typically managed by guidelines of the American College of Rheumatology,[5] American College of Physicians and the American Pain Society.[6] However, no consensus guidelines exist for the treatment of patients who do not respond to, cannot tolerate, or are not appropriate candidates for traditionally recommended treatments. Furthermore, even when standard treatments are effective, side effects and risks are significant. Up to 50% of patients treated with non-steroidal anti-inflammatory medications or opioids, experience gastrointestinal side effects[7]. Opioid treatment is associated with frequent adverse effects including abuse, mental impairment, tolerance, nausea and constipation resulting in over 20% discontinuing medication [8] and about 40% are non-adherent to the physicians recommended dose.[9]

Alternative therapies, such as acupuncture and massage, have become widely used in patients when traditional medical treatments for chronic pain are not effective, medically contra-indicated, poorly tolerated or simply refused.[10] The traditional herbs boswellia serrata, urtica dioica, equisetium arvensae, apium graveolens and allium sativum have been demonstrated to have activity at several anti-inflammatory pathways. Boswellia has been shown to be effective in reducing pain from osteoarthritis [11, 12][[13] , surgical tendon repair,[14] repetitive use arthritis [15] and in human mechanical pain models.[16] Urtica dioica has been shown to be clinically effective in the treatment of arthritis.[17, 18] Equisetium arvensae reduces inflammation and has anti-nociceptive actions [19] [20] and has been shown to reduce neuronal pain transmission signals.[19] Apium graveolens extracts reduce inflammation and improves arthritic conditions [21]. Allium sativum bulb powder has specifically been shown to have analgesic effects in animal pain models.[22] The family of B vitamins is essential for proper nerve cell functions and combinations of vitamins B1, B6 and B12 have been reported to have analgesic effects and reduce pain associated with lumbar vertebral disease [23] back pain [24] and diabetic neuropathy.[25]

Inflammation

Since the ancient times of the Egyptians and Greeks, inflammation was understood simply as a normal, early, healing reaction of the body to a sudden (acute) injury. In fact, Hippocrates used the word 'edema' in the 5th century B.C. as part of his description of inflammation. In 30-45 BC Anulus Celsus described the four main signs of inflammation: pain, warmth, redness, and swelling. Galen (129-200 AD) later added a 5th sign of inflammation: loss of function.

The understanding of the inflammatory process was fairly static until the development of the microscope in the 16th century, and by late 1800's it had become clear that an important part of the inflammatory process is a result of functional changes in small blood vessels, platelets (they help stop bleeding), and white blood cells. More recently, in the 20th century, it has become clear that there are a large number of molecules involved in the inflammatory pathways. These molecules can be thought of as the 'foot-soldiers' of the immune response, as they communicate and relay information to the cells,

It is now widely recognized that inflammation plays a significant, and often central role, in most chronic illnesses. Because of this, an understanding of inflammation and the development of a comprehensive approach to inflammation is a necessary aspect of the approach to management of chronic illness, regardless of diagnosis. Often, but not always (e.g., atherosclerosis) inflammation presents with pain and so it is included as the central clinical manifestation of inflammation for the purposes of this review.

The Molecules of Pain and Inflammation:
The molecules listed below are a small sampling of the molecules involved in inflammation.

a) Cytokines are a large, loosely defined group of small proteins that communicate signals between cells. One can think of cytokines as 'the hormones of the immune system', which communicate messages from one cell to the surface of another cell. It is now known that various member of this family promote inflammation (e.g., IL-1, IL-2, IL-6), while others reduce inflammation. Together the two groups keep the immune system in balance. Cytokines are crucial for fighting infection, but become significantly imbalanced with chronic illness, infections, physical or psychological trauma, etc.

b) **Tumor Necrosis Factor (TNF-Alpha)**-Tumor Necrosis Factor is a cytokine that has a wide variety of functions. It can cause cytolysis of certain tumor cell lines; it is involved in the induction of cachexia; it is a potent pyrogen, causing fever by direct action or by stimulation of interleukin-1 secretion; it can stimulate cell proliferation and induce cell differentiation under certain conditions. Sitting on the surface of certain cells, TNF-alpha receptor can become activated and send signals to the molecules inside the cell, ramping up the inflammatory cascade. TNF-alpha can become overly active by many stimuli, including high blood sugar.

c**) Nuclear Factor B (NF-Kappa B)**-This is an interesting 'family' of five proteins which sit inside the cell, but outside the nucleus of the cell (genes are located in the nucleus of the cell). When molecules such as TNF-Alpha signal the cell, some of the NF-Kappa B family members go into the cell nucleus. That is why it is called *nuclear* factor Kappa-B (abbreviated as NF-Kappa B). What is fascinating (to me at least) is that depending on the signal, different family members go into the nucleus, and turn on different genes. The result is that the genes produce a carefully orchestrated 'symphony' of many molecules of inflammation. Different signals received by the cells, produce through the NF-Kappa B, a different symphonic pattern of inflammatory molecules. This NF-Kappa B pathway is a "key regulator of inflammation".[26]

It is important to note that elevated levels of NF-Kappa B are found in many inflammatory diseases such as inflammatory bowel diseases, arthritis, and atherosclerosis (among others).

d) Matrix Metalloproteases (MMP's)-these zinc containing molecules (so far there are 23 members of this family) were identified to function in the break down of the 'cement' (called the extra-cellular matrix) which hold cells together. MMP's assist in remodeling of tissue after injury, but also are

involved in tissue damage, and breakdown of the molecules of inflammation, when chronically activated by inflammation.

e) **Arachidonic acid (AA)**- a fatty acid, which sits in the skin (cell membrane) of all cells. AA which exerts a key influence on how effective and efficient various signal molecules (such as cytokines) can be when communicating with another cell. In addition however, AA can be transformed into 3 groups of inflammation causing molecules called prostaglandins, leukotirenes with the help of enzymes called cyclooxygenase (COX 1 and COX 2) and lipoxygenase (LOX). If the AA is acted upon by COX 1 and 2, prostaglandins are produced, and if the AA is acted on by LOX, leukotrienes are produced.

f) Leukotrienes are a family of molecules regulate inflammation either within the cells that produce the leukotrienes themselves, or the cells that are nearby. Leukotrienes are associated with contraction of the smooth muscles in the lung (asthma), allergic reactions, and tissue secretion (e.g., nasal mucus).

g) Human Leukocyte Elastace-this is an enzyme (again, like many of the other molecules we are discussing here, this is one member of a family) which breaks down the matrix between cells. It is thought that it may play a role in degenerative and inflammatory diseases.

h) Prostaglandins-a group of fats derived from the fatty acid, Arachidonic Acid (above), the prostaglandins, which promote inflammation, are produced by the action of COX 2 on Arachidonic Acid; Prostaglandins have many functions (at least 10), including effects on inflammation. Levels of prostaglandins go up in inflammation, and they contribute to all the symptoms and signs of the inflammatory response.[27]

Prostaglandin D2 is involved in the regulation of sleep, pain perception, allergic reactions, cytokine production, Drugs like Aspirin, Advil, Aleve, Celebrex (non-steroidal anti-inflammatories) and Tylenol prevent prostaglandin production.

Cyclo-oxygenase-2 (COX-2) is the main enzyme that causes the production of prostaglandins in inflammation.

i) iNOS-this is an enzyme that leads to increased nitric oxide (NO). Nitric oxide is simple molecule which signals is involved in dilating blood vessels, something that is helpful in acute inflammation. At normal levels, NO reduces inflammation, however when NO is increased above normal levels, its role is reversed and it increases inflammation[28] by causing increased blood flow into tissues resulting in swelling (e.g. knee feeling swollen). Also, when NO is increased it can lead to changes in the balance of neurotransmitters in the brain, causing anxiety, excitability, and insomnia, and deterioration of nerve cells.

j) C-Reactive Protein: this is a protein that goes up when there is acute inflammation, caused, for example, by an infection. The liver makes C-reactive protein, and when there is acute inflammation, c-reactive proteins bind to the surface of dead or dying cells, so that they can be disposed of.

k) Free radicals:
a) damage parts of the cell including the energy factories of the cell (mitochondria)
b) damage to membranes resulting in poor cell to cell communication, which in turn leads to excessive glutathione usage, Vitamin B2, and NADH. Glutathione is one of the main anti-oxidants in the body used to reduce the damaging effects of too many free radicals and increases NADH usage (leading to a reduction of energy).

Inflammatory Cascades and Inflammatory Networks
Like a series of dominos the molecules listed above send instructions to cells, blood vessels, and ultimately to genes, controlling inflammation. An example of an inflammatory cascade is:

TNF-Alpha→ NF-Kappa-Beta→ Changes in Gene Function→ production of Inflammatory molecules such as cytokine IL-6→ Increased free radicals→ Damage to mitochondria, and membranes**.**

While cascades imply a linear "A" causes "B" model-like the dominos I mentioned above, in reality inflammatory pathways and their causes operate as complex interconnected network, every part affecting every other part, to a greater or lesser degree. The good news about this is that there are many counterbalancing systems that can adapt to stress, injury, and inflammation. The bad news is that chronic inflammation can affect the entire body, and bring out genetic vulnerabilities for disease.

Systems, Sources and Correlates of Chronic Inflammation

The systems that are involved in inflammation fall into a matrix consisting of 8 nodes, which interact with each other. These nodes are structural (e.g., musculoskeletal), digestion & nutrition, immune/infectious, detoxification processes, oxidative stress and mitochondrial function, neuro-hormonal, genetics and epigenetics, and psychosocial. As an example of the interaction between these nodes, a chronic stressor (e.g., unemployment) can eventually lead to a state of low cortisol production. Since cortisol helps control the function of the immune system(preventing excess inflammation), low cortisol can result in increased levels of inflammation and create an environment, which is permissive to autoimmune disease. On the other hand high levels of cortisol cause vulnerability to infection. A comprehensive approach to chronic pain and inflammation requires an evaluation of each of these systems, while using additional adjunctive anti-inflammatory measures.

Components of the DrH Rejoint proprietary preparation

The DrH Rejoint formula was constructed to take reduce inflammation by working at multiple parallel and sequential points within the and along the inflammatory networks. The individual ingredients, their location of action, balance, source and extraction technique were all considered in the final formulation.

Urtica Dioica: Stinging Nettle

Background

Found in Africa, Europe, the United States and Canada, stinging nettle is a perennial plant that has been used as a medicinal agent since ancient times. The genus name Urtica comes from the Latin verb urere, meaning, "to burn," because of its urticate (stinging) hairs that cover the stem and underside of the leaves, which can cause an inflammatory skin response. The species name dioica means "two houses" because the plant usually has male or female flowers**.** This herb, which grows ubiquitously, is often considered a weed, yet there is a great deal of research indicating it has very potent anti-inflammatory properties.

History:

According to secondary sources, nettle was used as a medicinal agent as early as 3 BC both internally and externally, mainly as a treatment or antidote for bites, wounds, and poisonings. Nettle was smoked to treat asthma. Native Americans used nettle tea for pregnancy complications and to stop uterine bleeding after childbirth. The early settlers adopted these uses and used it to increase breast milk production. The juice of the nettle leaf was believed to be a hair growth stimulant.

Constituents of Stinging Nettle

More than 100 chemical components have been identified in the hairs, roots, leaves and rhizomes of nettle. Amines, such as acetylcholine, 5-hydroxytryptamine (serotonin), and histamine are found in the stinging hairs; adrenaline and noradrenaline are in the chloroplasts. [29] Carotenoids, such as chlorophyll, xanthophyll, and beta-carotene have been identified in the herbage of fresh and dried plants [30] Vitamins A, B_1, B_2, B_9, C, E, and K have been identified from fresh and/or dried plant sources. Other components, such as cytokines, leukotrienes, scopoletin, volatile oils, rutin, ketones, ceramides, amino acids, glucokinins, mucilages, phospholipids (betaine, choline, lecithin), and

glucoquinones have all been identified in nettle preparations [31] [29] [30]. In the leaves of Urtica dioica, water-extractable magnesium, manganese, and copper have been identified.[32]

Mechanisms of Action:

Analgesic Effects

In a randomized controlled double-blind crossover study, stinging nettle demonstrated an analgesic effect and reduction of disability after one week of daily treatment. However the mechanism of action is unclear.[18].

Anti-inflammatory Effects

The proposed use of stinging nettle in the treatment of arthritis and inflammation may be due to components found in the extract of the root. A fraction of an aqueous extract containing polysaccharides demonstrated prolonged anti-inflammatory activity in the rat paw edema test. Some of the polysaccharides isolated from this fraction stimulated T-lymphocyte proliferation or influenced the complement system [31] [33]. An ethanolic extract was found to potently suppress human leukocyte elastase (HLE). HLE is one of the most destructive enzymes released by polymorphonuclear granulocytes, which migrate into tissues during the inflammatory process [34].
The water-soluble fraction of stinging nettle leaf extract (IDS 23 - Rheuma-Hek ®, Germany) demonstrated a dose dependent inhibition of phytohemagglutinin-stimulated production of Th1-specific interleukin-2 and interferon-gamma in peripheral blood mononuclear cells. [35] Inflammatory responses are primarily mediated by Th1 cells. IDS 23 has also demonstrated inhibition of leukotriene and prostaglandin syntheses [36] reduction of tumor necrosis factor-alpha (TNF-alpha) and interleukin-1beta (IL-1beta) in lipopolysaccharide-stimulated human whole blood [36] and inhibition of nuclear factor-kappaB (NF-kappaB) [17] The NF-kappaB family of transcription factors is critical for the inducible expression of many genes involved in inflammatory responses [17] and thus its use as a antirheumatic remedy may be dependent on its ability to inhibit the proinflammatory transcription factor NF-kB. A hydroalcoholic extract of stinging nettle was found to lower levels of interleukin-6 and high-sensitivity C-reactive protein (hs-CRP), but it lacked significant effects on TNF-alpha.[37]

Finally, Teucher et al. studied the effect of Urtica dioica extract on cytokine secretion in 20 volunteers and found out that ingesting two capsules of nettle leaf extract twice daily for 21 days resulted in a decrease of lipopolysaccharide-stimulated TNF-alpha and IL-1beta releases in whole blood.[38]

Safety

Stinging nettle root has been used safely for up to 2 years.[39] Stinging nettle root extract (Bazoton-uno) has been shown to be safe and effective in randomized, controlled long-term treatment study of benign prostatic syndrome (BPS).[40]

Adverse Effects:

Gastrointestinal

Continual pain in the gastrointestinal tract and hyperperistalsis were reported in one patient in an equivalence trial of 134 patients when two capsules of Prostatonin Pharmaton® were administered daily for eight weeks.[41] Seven patients taking a freeze-dried preparation of Urtica dioica capsules for the treatment of allergic rhinitis in a randomized controlled trial reported mild gastric discomfort when the medication was taken on an empty stomach.[42] Three of 10 patients in a case series treated with Urtica extract three times daily complained of gastrointestinal side effects that prompted withdrawal from the study.[43] Four of 25 patients treated with Urtica capsules in a randomized

controlled trial withdrew from the study due to side effects such as constipation, diarrhea, and gastric disorder.[44]

Hematologic
According to secondary sources, stinging nettle may decrease coagulation and cause hemorrhage. The nettle plant contains a substance that is a Coumadin derivative. [45] [31] [30] In a chronic toxicity study, nettle infusion was administered to Wistar rats via an intragastric probe. [45] The rats exhibited nasal, oral, and orbital bleeding. Upon autopsy, pulmonary edema and blood at the intestinal lumen were found. Coagulation time was delayed for seven days in the rats and was also determined to be the cause of death. Stinging nettle contains a significant amount of vitamin K [46] Therefore, there is some concern that stinging nettle might decrease the effects of anticoagulant drugs such as warfarin (Coumadin).

Interactions with Food
None known

Effect on Lab tests
None Known

Pharmacokinetics
After oral administration of 20 mg of Urtica dioica agglutinin (UDA) to healthy volunteers, 30-50% of the dose was excreted in the feces.[31] The total amount of UDA in the urine was less than 1%.

EVIDENCE
Arthritis
Summary: Nettle is widely used throughout Europe and in Australia as a folk remedy to treat arthritic and rheumatic conditions. Preclinical evidence and in vitro and in vivo effects suggests that certain constituents in the nettle plant have anti-inflammatory and/or immunomodulatory activity.[47] A combination trial evaluating Phytalgic (fish oil, vitamin E, and Urtica dioica) reported a decrease in NSAID and analgesic use and improvement in osteoarthritis (OA) symptoms. [48]
Christensen et al. commented on this trial and reported that the results from this trial are promising.[49] Well-designed, randomized controlled trials are needed to further support its use in humans.

Evidence: Rayburn et al. conducted a nonrandomized, uncontrolled, before-and-after comparison study to assess the effect of a prepared topical cream containing stinging nettle (Urtica dioica) on joint function due to osteoarthritis (OA) (N=23) [50] Stinging nettle cream for osteoarthritis. Individuals were included if they presented with radiologically confirmed OA. Further information on inclusion and exclusion criteria was lacking. Participants were instructed to apply a formulated topical stinging nettle cream twice daily for two weeks. The stinging nettle cream was prepared by compounding 13.33% (w/w) stinging nettle extract (Liquid Phyto-Caps Nettle Leaf®) in Lipobase® oil-in-water emulsion. The study reported that two participants experienced temporary tingling and mild discomfort. Information regarding toxic effects, dropouts, and interactions was lacking. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to measure any effect on the participants' joint function. Assessments were conducted at baseline and at the end of the two-week study period. A mean reduction in WOMAC score of 4.17 (95% CI: 1.87, 6.48) from a mean baseline score of 17.22 was observed following treatment with stinging nettle. Limitations of this study included the lack of a control group. Patient inclusion criteria and exclusion criteria were also inadequately described, thus further limiting the study's generalizability. Moreover, patient medication information was lacking. In addition, the sample size was small, and the treatment period was only two weeks.

Chrubasik et al. conducted an open, equivalence trial comparing diclofenac 50 mg plus stewed stinging nettles (D50+U) to diclofenac 200 mg (D200) in the treatment of an acute attack of chronic joint

diseases (N=40). [51] Patients were randomly assigned to receive diclofenac 100 mg twice-daily plus misoprostol or diclofenac 50 mg (in capsules identical to the D200 group) plus placebo for 14 days. Study participants were offered the same nutrition, except that the diclofenac 50 mg patients also received 50 g of stewed nettle using the leaves of young Urtica dioica. The primary outcome measure was improvement in elevated C-reactive protein (CRP). Secondary outcomes were total joint scores for physical impairment, subjective pain, and pain on pressure as assessed by the patient, and stiffness assessed by the physician. The median CRP concentration decreased to 68% of baseline level in the diclofenac 200 mg group and to 71% in the diclofenac 50 mg-plus-nettle group (p=0.34). The change in the median scores of patient and physician assessments decreased similarly in both groups for the following: physical impairment (67% for D200 and 60% for D50+U, p=0.71); subjective pain (67% for D200 and 77% for D50+U, p=0.38); pressure pain (75% for D200 and 77% for D50+U, p=0.66); and stiffness (52% for D200 and 67% for D50+U, p=0.38). Diclofenac 50 mg with 50 g of stewed Urtica dioica produced an effect on CRP and clinical symptoms of acute arthritis similar to diclofenac 200 mg. The results of this study would have been stronger if a third group receiving only diclofenac 50 mg had been included to serve as a control group and establish diclofenac 50 mg as a subtherapeutic dose in the treatment of arthritis.

Select combination studies (not included in the Evidence Table): Jacquet et al. conducted a randomized, double-blind, placebo controlled clinical trial to evaluate the effects of Phytalgic® in patients with knee and hip OA (N=81).[48] Patients included in the trial had knee or hip OA and were using NSAIDs and/or analgesics. Patients randomly received Phytalgic® (fish oil, vitamin E, and Urtica dioica) vs. placebo daily for three months. The primary outcome measures included use of NSAIDs by defined daily doses per day (DDD/day), use of analgesics defined in 500 mg paracetamol (acetaminophen)-equivalent tablets per week (PET/week), and WOMAC function scales. Those taking Phytalgic® for three months significantly decreased their mean use of analgesics by 6.5 PET/week vs. 16.5 PET/week (p<0.001; mean difference of -10.0; 95% CI: -4.9 to -15.1), and decreased use of NSAIDs to 0.4 DDD/day vs. 1.0 DDD/day (p=0.02; mean difference of - 0.7 DDD/day; 95% CI: -0.2 to -1.2). Mean WOMAC scores evaluating pain, stiffness, and function reported significant improvement in those taking Phytalgic® (86.5, 41.4, and 301.6, respectively) vs. placebo (235.3, 96.3, and 746.5, respectively) (p<0.001; mean differences, respectively, of -148.8 (95% CI: -97.7 to -199.9), -54.9 (95% CI: -27.9 to -81.9), and -444.8 (95% CI: -269.1 to -620.4)). Symptoms of osteoarthritis improved and NSAID and analgesic use decreased in patients taking Phytalgic®. Further details are lacking. The effect of Urtica dioica alone is unclear. Christensen et al. commented on this article and reported that the results from this trial are promising.[49]

Inflammation

Summary: According to a randomized clinical trial, 100 mg/kg of stinging nettle daily for eight weeks made a significant difference compared to placebo in lowering inflammatory markers such as IL-6 and hs-CRP, but not on TNF-alpha.[37] Further well-designed clinical trials are needed before conclusions can be made.

Evidence: Namazi et al. conducted a randomized, double-blind, placebo controlled trial to assess the effects of a hydroalcoholic extract of stinging nettle (Urtica dioica) on insulin sensitivity and markers of inflammation (N=50).[37] Participants were included if they were over the age of 30 years, had a glycosylated hemoglobin (HbA_{1c}) level =10%, used common diabetes drugs, and had triglyceride levels <400 mg/dL. Participants with cardiovascular, kidney, liver or thyroid diseases; infections; allergies; or angina were excluded. Also, if individuals were taking nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, or insulin, as well as if they used alcohol, herbal teas, or dietary supplements, they were also excluded. Participants were randomized to receive 100 mg/kg of stinging nettle extract or placebo in three portions daily. Each portion was to be dissolved in one glass of water and consumed after a main meal for duration of eight weeks. Each liter of hydroalcoholic extract of stinging nettle contained 45% ethanol, 55% water, and 2.7g of dry matter. Water and alcohol percent in placebo was equal to the stinging nettle extract, with the additions of chlorophyll color to eliminate differences in appearance. Information regarding adverse and toxic effects was lacking. Five participants failed to

complete the study, but information regarding the reasons for the dropouts was lacking. Interaction information was lacking. Biomarkers of inflammation, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and high-sensitivity C-reactive protein (hs-CRP), were measured. In addition, concentrations of insulin were measured to assess insulin sensitivity, and changes in body mass index (BMI) and waist circumference were assessed. Compared to the placebo group following treatment, participants treated with stinging nettle had significantly lower levels of IL-6 (3.49 ± 0.54 vs. 1.19 ± 0.27 pg/mL, $p<0.01$) and hs-CRP (2.95 ± 0.87 vs. 1.37 ± 0.11 mg/dL, $p=0.03$). A statistically significant between-group difference regarding levels of TNF-alpha or insulin sensitivity was lacking after treatment. In addition, there was a lack of between-group difference regarding changes in BMI or waist circumference. Limitations of this study included the lack of information regarding dropouts, adverse and toxic effects, and interactions. This trial was also performed at one facility in Iran. Moreover, further information regarding ethnicities, length of time of having type 2 diabetes, and concurrent diabetes medications used by participants was lacking, which may limit the generalizability of the results.

Joint pain

Summary: Nettle has historically been used in several different forms to treat pain of varying origins. Randall has conducted several studies that evaluated stinging nettle's effect on osteoarthritis pain, and although a recent trial did not show significant differences compared a the control group, the other trials had reduction in visual analog pain scores and pain relief experienced by most participants.[18, 52, 53]

However, well-controlled statistically significant clinical trials to support this use are lacking.

Evidence: Randall et al. conducted a randomized, single-blind, controlled trial to assess the effect of stinging nettle (Urtica dioica) on chronic knee pain (N=42) [52] Individuals who visited practices within the Plymouth Primary Care Trust with at least three partners and computerized record systems were recruited. Age parameters were being 55-80 years old. Individuals were included if they had a presumptive diagnosis of osteoarthritis of the knee based on the American College of Rheumatology (ACR) clinical criteria and were able to complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire. They also had to report a score of greater than 4 on the pain subscale at baseline. Individuals were excluded if their general practitioner thought they were unsuitable, or if they were unable to comprehend the instructions, lacked a telephone number recorded in the medical notes, were already in a clinical trial, were receiving steroid treatment (oral or intra-articular), had used stinging nettle for joint pain in the previous three months, had an allergy to nettle, or were taking antihistamines. Individuals were also excluded if they had a history of severe systemic conditions, including diabetes, rheumatoid arthritis, a major psychiatric disorder, a separate significant painful condition, any condition of the skin of the knee, previous or intended knee replacement surgery (in the painful knee), or recurrent eczema. Individuals were allocated into a treatment group receiving Urtica dioica or an equivalent control group receiving Urtica galeopsifolia. Leaves from the respective nettle plants were applied to the painful knee for about 10 seconds. This was repeated twice, using alternate sides of the leaf, at different locations of the knee. This procedure was then repeated using a fresh leaf. Individuals used the leaves for a total of seven days. Standardization was reported to be similar to the highest dose used in practice; however, additional specific information was lacking. Three patients in the treatment group reported adverse reactions that included an itchy rash on the arm and blistering at the application site. Also, one participant reported that the stinging due to treatment was severe and lasted about 12 hours. One patient in the control group reported stiffness in the treated leg. Information on severe adverse or toxic effects was lacking. Two individuals in the treatment arm and five in the control arm were lost to follow-up, and reasons included personal reasons (N=1), feeling unwell (N=3), and a steroid injection (N=3). Information regarding interactions was lacking. The primary outcome measured was difference in WOMAC pain score. This outcome was assessed after one, four, and 16 weeks of treatment. Secondary outcomes included the remaining WOMAC subscales, as well as the participant's acceptance of the treatment, which was assessed by a focus group at 16 weeks. Both groups showed a reduction in WOMAC pain scores following treatment, but a between-group difference regarding these

changes was lacking. Also, between-group differences regarding stiffness or function scores were lacking after treatment. Only six individuals participated in the focus group. Most of these individuals were unconcerned about the minor stinging, although one reported that the stinging was severe. Limitations of this study included a lack of information on standardization, as well as specific baseline characteristics and any medications being administered. This was also a study performed with an equivalent control that lacked the stinging characteristic, which may have limited the blinding that was intended.

Randall et al. conducted a randomized, controlled, crossover study assessing the efficacy of nettle sting for the treatment of osteoarthritic pain at the base of the thumb or index finger (N=27).[18] Patients with persistent pain were randomized to receive a nonflowering nettle leaf or white deadnettle leaf (placebo). Patients were instructed to cut a leaf and apply the underside of the leaf to the painful area with gentle pressure for about 30 seconds, moving the leaf twice. This was to be done once daily. Patients treated themselves at home for one week then returned to the clinic for assessment. After a five-week washout, patients were crossed over to the opposite group and again self-treated for one week. The key outcome measures were the visual analog pain scale and health assessment questionnaire scores. The visual analog pain scores for the treatment group fell lower than those for placebo at day 2 and remained so for the remainder of the week (-14.63 vs. -0.45; p=0.026, 95% CI: -0.02 to 30.72). The health assessment questionnaire scores for stinging nettle showed a significant reduction compared to placebo (-0.17 vs. -0.04; p=0.0027; 95% CI: 0.07-0.352). Localized rash and slight itching occurred in 23 of 27 patients. Stinging nettle demonstrated an analgesic effect and reduction of disability after one week of daily treatment. One weakness in the design of this study was the incomplete blinding; some patients reported stinging only with one plant treatment. In addition, application of the juice was uncontrolled. Since patients were self-administering nettle, different patients may have used different amounts, which could have affected efficacy. Randall et al. conducted a retrospective cohort study to investigate the efficacy of nettle in relieving joint pain (N=18).[53]

Subjects with personal experience of external use of nettle for pain relief were recruited for the study and interviewed about their use of nettle as a pain relief medication, their method of use and its efficacy. Stroking, beating, and pressing leaf on affected areas were the methods of application subjects had used for different durations and frequencies. All patients but one reported pain relief after the first course of treatment. Fifteen patients claimed that nettle worked on every application, rendering pain relief in less than 24 hours, and two said it was effective about 90% of the time. Analgesic effect was claimed to be most effective if a sting with wheals was produced, and the treatment repeated daily for several days. Rigorous, randomized, double-blind, controlled trials are still needed to evaluate the role of nettle in pain management.
Randall et al. reported a case study on the efficacy of stinging nettle for osteoarthritis of the hip (N=1).[54]
A healthy man aged 81 years had pain over the left hip joint for six months. His X-ray showed definite osteoarthritis and joint space narrowing. He was prescribed ibuprofen, which did not provide adequate pain relief. The patient applied stinging nettle leaves to the region of his left hip for some weeks and noticed a remarkable improvement. He was eventually able to stand on either leg and was riding his bicycle up to 10 miles daily with no pain with the application of nettle every few days.

BOSWELLIA SERRATA

History

Boswellia serrata is an herb used for millennia and for good reason. In fact, its use is described in biblical texts written around 586 BCE. While used in religious ceremonies (it was used for its aromatic effects), it was very likely also used for its anti-inflammatory pain relieving effects.. Extracts from resins of Boswellia species have been used for years in African countries and in Ayurvedic medicine in India for the treatment of a variety of diseases. [55, 56] Frankincense is also derived from Boswellia

species. Today, Boswellia is often used in complementary medicine, most commonly for inflammatory conditions such as rheumatoid arthritis.

Constituents
Boswellia is frequently standardized according to the boswellic acid content.[57] The gum resin typically contains 30% boswellic acids, while ethanol extracts contain 43% boswellic acids.[58] Some commercial sources contain up to 70% boswellic acids. The Boswellia serrata tree contains a gummy oleoresin found under the bark.[55]

The four major pentacyclic triterpene acids isolated from the gum resin of Boswellia serrata are beta-boswellic acid (the most abundant), 3-acteyl-beta-boswellic acid, 11-keto-beta-boswellic acid, and 3-acetyl-11-keto-beta-boswellic acid. These triterpenes are responsible for the pharmacologic effects. Individual triterpenoids included lupeol, beta-boswellic acid, 11-keto-beta-boswellic acid, acetyl beta-boswellic acid, acetyl 11-keto-beta-boswellic acid, acetyl-alpha-boswellic acid, 3-oxo-tirucallic acid, and 3-hydroxy-tirucallic acid.

Mechanisms of Action

Analgesic effects: Acetyl-11-keto-beta-boswellic acid is one of the four major pentacyclic triterpenic acids found in the gum resin of Boswellia serrata.[59] Acetyl-11-beta-boswellic acid is a highly specific inhibitor of 5-lipoxygenase, an enzyme for leukotriene biosynthesis.[60] [61] In animal research, dose-dependent analgesic activity has been noted. [62] A study in rats showed that the nonphenolic ration of Boswellia serrata gum resin (20-300 mg/kg) exhibited an analgesic effect similar to morphine (4.5 mg/kg).[63]

Anti-inflammatory effects: Multiple pentacyclic triterpenic acids, referred to as boswellic acids, have been isolated from resins of the Boswellia species and identified as major anti-inflammatory components of Boswellia gum resin extract.[55] Busheled, B. and Simmet, T. Analysis of 12 different pentacyclic triterpenic acids from frankincense in human plasma by high-performance liquid chromatography and photodiode array detection.[64-66] Acetyl-11-keto-beta-boswellic acid from Boswellia has been identified as one of the primary anti-inflammatory triterpenoid acids in Boswellia resin extract. Acetyl-11-beta-boswellic acid is a highly specific inhibitor of 5-lipoxygenase, an enzyme for leukotriene biosynthesis [60] [61] Animal research shows that it inhibits the release of leukotrienes B4 (LTB4) [55] [67] [68] Additional studies have found that Boswellia inhibits human leukocyte elastase (HLE).[67]

Doses of 50-200 mg/kg of Boswellia extract given orally to mice following the injection of an inflammatory agent into the intrapleural cavity inhibited polymorphonuclear leukocyte (PMN) infiltration, similar to the effect seen with indomethacin. Similarly effective anti-inflammatory activity has been observed in studies of rats with laboratory-induced paw inflammation, and in animal models with arthritis, gouty arthritis, and polyarthritis. Antipyretic activity in rats and rabbits has also been noted.

Results of studies suggest that Boswellia extract may also inhibit TNF-alpha-induced inflammatory response [69]. [70]. The effects of acetyl-11-keto-beta-boswellic acid (AKBA) on TNF-alpha-inducible metalloproteinase expression in human microvascular endothelial cells (HMECs) were evaluated in vivo and in vivo.[70] Treatment of HMECs for two days with either a 3% or 30% formulation protected against arthritis by preventing TNF-alpha-induced expression and activity of matrix metalloprotease-3 (MMP-3), MMP-10, and MMP-12. The 30% formulation was consistently more effective than the 3% formulation.

Earlier studies showed that boswellic acids reduced enzymes that are elevated in inflammatory conditions like arthritis, such as glutamic pyruvic transaminase, glycohydrolase, and beta-glucuronidase.[71-73] Inhibition of glycosaminoglycan (GAG) synthesis and urinary excretion of

connective tissue metabolites by boswellic acids may support the purported beneficial effects of Boswellia in the prevention of the degradation of connective tissue in inflammatory arthritic conditions.

In a study of mice with trinitrobenzene sulfonic acid-induced colitis, high doses of Boswellia extracts were ineffective at reducing inflammatory responses and were associated with hepatotoxic effects, including hepatomegaly and steatosis.[74] Based on these findings, the authors recommended that further research be conducted to elucidate the anti-inflammatory effects and potential hepatotoxic effects of Boswellia in humans.

Abdel-Tawab et al. published a review of Boswellia serrata.[75] The authors suggest that animal and pilot clinical research support its anti-inflammatory effects. They suggest that until recently, pharmacological effects of extracts were attributed to leukotriene formation suppression by the boswellic acids, 11-keto-ß-boswellic acid and acetyl-11-keto-ß-boswellic acid. This effect is lacking in human whole blood, and due to the poor pharmacokinetics, the authors suggest another mechanism is likely, such as the inhibition by beta-boswellic acid of microsomal prostaglandin E synthase-1 and the serine protease cathepsin G. In 2009, Tausch identified human cathepsin G as a potential functional target of boswellic acids using human blood ex vivo.[76]

According to a review, incensole acetate (a major component of Boswellia resin) is a nuclear factor (NF)-kappaB inhibitor.[77]

Pharmacokinetics

Food appeared to alter the pharmacokinetic profile of Boswellia.[78] Meals that are high in fat increased the concentration of beta-boswellic acid, 11-keto-beta-boswellic acid, and acetyl-11-keto-beta-boswellic acid, acetyl-alpha-boswellic acid, and alpha boswellic acid in plasma.

After a single 333 mg dose of Boswellia serrata extract, the mean elimination half-life was reported to be 5.97 ± 0.95 hours.[79] Metabolites of Boswellia appear to be excreted in urine.[80]

Pharmacokinetic tests of gum-resin of Boswellia carterii, Boswellia frereana, Boswellia sacra, and Boswellia serrata showed that they are moderate-to-potent inhibitors of CYP enzymes, with equal potency for inhibiting the major drug metabolizing enzymes 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4.[81]In 12 healthy volunteers who took a single 333 mg dose of Boswellia serrata extract (BSE), peak plasma levels (2.72×10^{-3}± 0.18 mm/mL) of BSE were reached at 4.5 ± 0.55 hours.[79]

Adverse Effects

Adverse effects were reported as being minimal in patients with rheumatoid arthritis who were given the standardized Boswellia extract A1.[82] According to a 2013 systematic review of herbal medicines, adverse effects of Boswellia serrata were minor.[83] According to the author of a clinical trial, serum, hematologic, and urine tests revealed a lack of major adverse effects.[84] Additionally adverse events were lacking in a systematic review or clinical trial.[85] In another trial, side effects were equivalent to placebo.[86]

The most common adverse effects in trials have been gastrointestinal-related, including nausea, epigastric pain, diarrhea, and acid reflux.[87-89]

There is poor evidence for moderate inhibition of CYP450 1A2 2C19, 2C9, and 3A4.[81]

Lab Interactions: None known

Evidence of Efficacy:

There is good quality evidence in support of the use of Boswellia for OA.[84, 85, 87, 90-92][93]Ernst conducted a systematic review to assess evidence from randomized clinical trials about the effectiveness of extracts of Boswellia serrata (frankincense). [90] Electronic searches on MEDLINE, Embase, CINAHL, AMED, and the Cochrane Library were conducted, as were manual searches of conference proceedings, bibliographies, and departmental files. All randomized clinical trials of Boswellia serrata extract as a treatment for any human medical conditions were included, and studies of Boswellia serrata preparations combined with other ingredients were excluded. Selection of studies, data extraction, and validation were done by the author. The Jadad scoring system was used to evaluate the methodological quality of all included trials. Of 47 potentially relevant studies, seven met all inclusion criteria (five placebo controlled, two with active controls). The included trials related to osteoarthritis [84, 87, 93] and collagenous colitis.[94] The results of all trials indicated that Boswellia serrata extracts were clinically effective. Three studies were of good methodological quality. Serious safety issues were not noted.

Sengupta et al. conducted a three-group, randomized, placebo controlled trial to evaluate the safety and efficacy of 5-Loxin® in treating OA of the knee (N=75).[84] Participants were outpatients who had OA for more than three months and were included if they were between 40 and 80 years of age, met the American College of Rheumatology classification criteria, were taking prescription strength nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen regularly for 30 days before the trial with benefit, and, after withdrawal from usual medication, had visual analogue scale (VAS) scores between 40 and 70 mm and a Lequesne's Functional Index (LFI) score greater than seven points. Subjects were excluded with a history of inflammatory arthropathy or rheumatoid arthritis (RA), hyperuricemia (>440 mcM/L), history of peptic ulcer or upper gastrointestinal bleed, or body mass index >30 kg/m^2. Patients in the low dose 5-Loxin® group received 50 mg; patients in the high dose 5-Loxin® group received 125 mg; patients in the placebo group received one similar capsule filled with rice bran. All doses were in capsule form and were given twice daily by mouth for 90 days. 5-Loxin® is extracted from Boswellia serrata enriched to 30% 3-O-acetyl-11-keto-beta-boswellic acid (AKBA). Reports of toxic effects in study participants were lacking. The primary outcome measures were pain, physical function, and joint stiffness. Statistically significant improvements in the low dose group vs. placebo on the VAS, LFI and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores were 48.83% ($p<0.001$), 23.79% ($p<0.036$), and 39.61% ($p= 0.009$), respectively. Statistically significant improvements in the high dose group vs. placebo on the VAS, LFI, WOMAC pain, WOMAC stiffness, and WOMAC function were 65.94% ($p< 0.001$), 31.34% ($p<0.017$), 52.05% ($p< 0.001$), 62.22% ($p= 0.014$), and 49.34% ($p= 0.002$), respectively. In general, this was a small, well-conducted, 90 day, double-blind, randomized, placebo controlled study.

Sengupta et al. also conducted a randomized, double-blinded, placebo controlled trial to determine the effects of 5-Loxin® and Aflapin® for OA of the knee (N=60) [92] Participants were included in the study if they were between the ages of 40 and 80 years with OA of the knee for three months or longer, and after a week without medication had a VAS score for pain of 40-70 mm. Compared to placebo, the Aflapin® treatment group had significantly superior improvements in VAS (47.3%, $p<0.0001$), LFI (35.8%, $p=0.0004$), WOMAC pain (61.7%, $p<0.0001$), WOMAC stiffness (60.1%, $p=0.0001$), and WOMAC functional ability (49.4%, $p=0.0001$) at the end of the study. The authors concluded that 5-Loxin® and Aflapin® were effective and safe for OA of the knee.

Kimmatkar et al. conducted a randomized, double-blind, placebo controlled, crossover trial in 30 patients to assess the safety and efficacy of Boswellia serrata in patients with osteoarthritis of the knee.[87] Subjects were administered either a placebo or a formulation of Boswellia serrata extract 333 mg three times daily (standardized to 40% to 40% total boswellic acid [87] Reduction in the severity of pa in and swelling and improvement in the loss of function were significant in the group receiving the Boswellia serrata treatment vs. the placebo ($p<0.001$). Decreased knee pain; increased knee flexion; increased walking distance; improvement in range of movement of the knee, walking up

stairs, and squatting; and better ability to kneel and sit cross-legged were also noted in those receiving Boswellia.

Sontakke et al. conducted a randomized, prospective, open-label, comparative study to compare the efficacy, safety, and tolerability of Boswellia serrata extract to valdecoxib in patients with osteoarthritis.[93] Sixty-six subjects, aged between 40 and 70 years, were randomly assigned to receive Boswellia serrata extract (BSE) 333 mg three times daily (N=33) or valdecoxib 10 mg once daily (N=33) for six months. The WOMAC scale was used to assess patients at baseline and at one-month intervals until one month after drug discontinuation. In the BSE group, pain, stiffness, and difficulty in performing daily activities showed statistically significant improvement with two months of therapy; this even lasted until one month after stopping the intervention ($p<0.001$). In the valdecoxib group, the statistically significant improvement in all parameters was reported after one month of therapy, but the effect persisted only as long as the drug therapy continued ($p<0.001$).

EQUISETUM ARVENSAE

Background

Horsetail (Equisetum arvense) has traditionally been used in Europe as an oral diuretic for the treatment of edema. The German Commission E expert panel has approved horsetail for this indication. Horsetail is also occasionally used for osteoporosis, nephrolithiasis, urinary tract inflammation, and wound healing (topical). These uses have largely been based on anecdote and clinical tradition rather than scientific evidence. Orally, horsetail is used for diuresis, edema, kidney and bladder stones, urinary tract infections, incontinence, and general disturbances of the kidney and bladder. It is also used for alopecia; tuberculosis; jaundice; hepatitis; brittle fingernails; rheumatic diseases; gout; osteoarthritis; osteoporosis; frostbite; weight loss; menorrhagia; and nasal, pulmonary, and gastric hemorrhage.

Topically, horsetail is used for treatment of wounds and burns.

Constituents

The benzoic acid derivative hippuric acid and the quercetin derivative homovanillic acid are metabolites of Equisetum arvense.[95]

Adverse Effects

Horsetail contains thiaminase, an enzyme that can cause thiamine deficiency.[96]
Abdominal distension, increased frequency of bowel movements, and nausea were noted in a trial of horsetail for nephrolithiasis.

Drug Interactions:

Some evidence indicates horsetail may lower blood sugar.[97] Animal research suggests that horsetail has diuretic properties.[98] Theoretically, due to these potential diuretic effects, horsetail might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased. Horsetail contains chromium (0.0006%) and could increase the risk of chromium toxicity when taken with chromium supplements or chromium-containing herbs such as bilberry, brewer's yeast, or cascara.[99]

Mechanism of Action:

Antioxidant effects: Equisetum telmateia may be a useful source of antioxidants with huge scavenger ability.[100]

Diuretic Effect: Horsetail possesses weak diuretic properties, which are believed to be due to equisetonin and flavone glycosides. In one human trial examining patients with a history of

nephrolithiasis, an 18-24% statistically significant increase in diuresis was noted in those taking horsetail vs. baseline after 8-12 weeks; these individuals had an increase in glomerular filtration rate (GFR) of 22%.[101] Horsetail was also noted to lower urine pH. Renal excretion of uric acid increased as did urine uric acid crystal formation.

Hepatoprotective effects: The phenolic petrosin onitin and flavonoid luteolin isolated from Equisetum arvense L. (Equisetaceae) exhibited hepatoprotective activities on tacrine-induced cytotoxicity in human liver cells, displaying EC_{50} values of 85.8 ± 9.3 mcM and 20.2 ± 1.4 mcM, respectively.[102]

Steroidal effects: Sterols contained in Equisetum arvense include beta-sitosterol, campesterol, isofucosterol, and trace amounts of cholesterol.[103]

ALLIUM SATIVUM

Background
Allium Sativum, commonly known as garlic is a culinary herb cultivated worldwide. It is related to onion, leeks, and chives. It is thought that garlic is native to Siberia, but was spread to other parts of the world over 5000 years ago.

People Use Garlic for:
Garlic is used for exercise performance, exercise-induced muscle soreness, osteoarthritis, joint pain, gout, gastrointestinal disorders, immune enhancement, stress and fatigue. Additionally, garlic is used for more than 50 other conditions.

Safety:
Garlic is safe when used orally and appropriately for up to 7 years. [104]

Constituents:
The applicable part of garlic is the bulb. The bulb of garlic contains the cysteine sulfoxide. Many of the pharmacological effects of garlic are attributed to the allicin, ajoene, and other alliin, also known as S-allyl-L-cysteine sulfoxide. Other garlic constituents include S-propylcysteinesulfoxide (PCSO) and S-methylcysteine-sulfoxide (MCSO), which can also be converted by alliinase to constituents such as allyl methane thiosulfinate, methyl methanethiosulfinate, and other thiosulfinates. Volatile constituents of garlic include diallyldisulfide (DADS), dimethyltrisulfide (DATS), and sulfur dioxide.[105]

Mechanisms of Action:

Antibacterial effects: Fresh garlic has shown activity against Escherichia coli, methicillin-resistant Staphylococcus aureus, and Salmonella enteritidis; it has been suggested as a food additive to prevent food poisoning.[106] The antimicrobial effects of garlic have been attributed to its allicin content.

Antioxidant effects: In various laboratory studies, garlic and its constituents displayed antioxidant activity, including increasing that activities of glutathione peroxidase, catalase, and superoxide dismutase; lowering xanthine oxidase activity; and inhibiting lipid peroxidation and prostaglandin production.[107-109]

Antiviral effects: Preliminary in vitro evidence suggests that garlic compounds, including ajoene, allicin, allyl methyl thiosulfinate, and methyl allyl thiosulfinate, might have activity against viruses such as cytomegalovirus, influenza B, herpes simplex virus type 1, herpes simplex virus type 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2. [110-113]

Immunologic Actions: Some in vitro evidence suggests that garlic powder extract reduces lipopolysaccharide-induced production of IL-1beta and tumor necrosis factor (TNF)-alpha in human whole blood. Garlic powder extract also appears to reduce the activity of nuclear factor (NF)-kB, a transcription factor involved in inflammation associated with autoimmune diseases such as arthritis and inflammatory bowel disease, as well as atherosclerosis.[114]

Evidence from animal research suggests that garlic oil 100-200 mg/kg every other day for 2 weeks enhances lymphocyte proliferation rate and increase the production of the cytokines interleukin 2 (IL-2), interferon gamma (IFN-gamma), IL-4, and IL-10 upon stimulation with concanavalin A.[115] At low doses, garlic oil appears to enhance T cell response toward the Th1 type cytokines (eg, IL-2 and INF-gamma).[115]

Garlic may also enhance natural killer (NK) cell number and activity.[116]

According to preliminary research, allicin (the major biologically active component of garlic) supplementation may reduce exercise induced muscle damage [117] Allicin supplementation for 14 days reduced plasma creatine kinase (CK), muscle-specific creatine kinase (CK-MM), interleukin-6 (IL-6), and perceived muscle soreness after exercise. Sixteen subjects were randomized to allicin supplementation (80 mg daily) or a control group for 14 days. Allicin supplementation resulted in reduced exercise-induced plasma creatine kinase (CK), muscle-specific creatine kinase (CK-MM), interleukin-6 (IL-6), and perceived muscle soreness after exercise when compared to placebo. It was also found to reduce muscle soreness.[117]

Ince et al. conducted a randomized, double-blind, placebo controlled, crossover trial to evaluate the effects of a single dose of garlic on aerobic performance in college endurance athletes. Ten subjects participated in the study and were given 900 mg of odor-modified dried garlic or placebo in a single administration. Heart rate, VO_2 max, and endurance time responses of each subject were recorded. VO_2max and mean endurance performance time for treadmill running increased significantly five hours after the ingestion of a single dose of garlic compared to placebo ($p<0.01$ and $p<0.001$, respectively). This study received a Jadad score of 2.[118]

Circulation
Summary: In observational research, garlic supplementation increased calf blood flow in healthy individuals. Moreover, the improvement was associated with and possibly mediated by increased plasma levels of interleukin-6 (IL-6). In this study, increased IL-6 was independent of the activation of the NO pathway.[119] [120]

Drug Interactions:
There is theoretical evidence that raw garlic and extracts can have anti-platelet activity and increase prothrombin time. Theoretically, garlic might enhance the effects and adverse effects of other anticoagulant and antiplatelet drugs, including aspirin, clopidogrel (Plavix), enoxaparin (Lovenox), warfarin (Coumadin), and others.[121]

Garlic and its extracts can reduce blood pressure. Theoretically, combining garlic with other blood pressure agents might cause additive hypotensive effects; use with caution. Some antihypertensive drugs include nifedipine (Adalat, Procardia), verapamil (Calan, Isoptin, Verelan), diltiazem (Cardizem), isradipine (DynaCirc), felodipine (Plendil), amlodipine (Norvasc), and others. [122]

There is theoretical evidence that garlic preparations may effect the metabolism of contraceptives via the effect on CYP450 3A4. This effect can, in theory impact the metabolism of numerous drugs.

Side Effects:

Garlic can irritate the GI tract; use with caution in individuals with infectious or inflammatory GI conditions.[123-125]

As mentioned above, garlic can lower blood pressure, and prolong bleeding time.

Lab interactions:
Garlic can increase INR in patients' anticoagulated with warfarin (Coumadin). There are two case reports of increased INR associated with concomitant use of garlic products and warfarin.[126]

APIUM GRAVEOLENS

Background
Apium graveolens, a herb from Europe and temperate parts of Asia, is a species in the family of *Apiaceae*. Wild celery (Apium) can be found throughout Europe, the Mediterranean, and parts of Asia. The leaves, stalks, root, and seeds can be eaten. Celery seed has also been used as a diuretic and to treat gout.

People Use This For
Orally, celery is used to treat rheumatism, gout, hysteria, nervousness, headache, weight loss due to malnutrition, loss of appetite, and exhaustion. Celery is also used as a sedative, mild diuretic, urinary antiseptic, digestive aid, menstrual stimulant, anti-flatulent, aphrodisiac, to reduce lactation, for regulating bowel movements, stimulating glands, for blood purification, dysmenorrhea. It was believed in Chinese folklore that *Apium graveolens* Linn alleviates hypertension, vertigo, headache, redness of the face and eyes, swelling and pain.

Safety
Celery seed has Generally Recognized as Safe (GRAS) status in the US (Electronic Code of Federal Regulations. Title 21. Part 182 -- Substances Generally Recognized As Safe.)

Constituents:
L-3-*n*-butylphthalide (L-NBP) is the active component of the essential oil extracted from the seeds of *Apium Graveolens.[127]*
Celery contains phenols and furocoumarins (psoralens). Celery tuber also contains methoxsalen (8-methoxypsoralen) and 5-methoxypsoralen and the allergen profilin (Api g 1), which shows high homology to birch pollen profiling[128] and thus can cross react with those who are allergic to birch pollen. It also contains flavonols (luteolin and apigenin).[129] Celery seed oil contains the natural phthalides.[130] Celery contains high amounts of sodium.[131]

Mechanism of Action
The anti-inflammatory activities of celery extracts, some rich in flavone aglycones and others rich in flavone glycosides, were tested on the inflammatory mediators tumor necrosis factor α (TNF-α) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) in lipopolysaccharide-stimulated macrophages. Pure flavone aglycones and aglycone-rich extracts effectively reduced TNF-α production and inhibited the transcriptional activity of NF-κB, while glycoside-rich extracts showed no significant effects. These results demonstrate that deglycosylation increases absorption of dietary flavones in vivo and modulates inflammation by reducing TNF-α and

NF-κB, suggesting the potential use of functional foods rich in flavones for the treatment and prevention of inflammatory diseases.[132]

Apigenin, a flavonoid abundantly found in fruits and vegetables, including celery, exhibits anti-proliferative and anti-inflammatory activities through inhibition of the production of proinflammatory cytokines IL-1beta, IL-8, and TNF in LPS-stimulated human monocytes and mouse macrophages. Apigenin inhibits the transcriptional activity of NF-kappaB in LPS-stimulated mouse macrophages as well. [133]

Food plants of the Apiaceae plant family such as carrots, celery and parsley, contain a group of bioactive aliphatic C17-polyacetylenes. These polyacetylenes have shown to be highly toxic towards fungi, bacteria, and mammalian cells, and to display anti-inflammatory and anti-platelet-aggregatory effects.[134]

Interactions with Drugs and other Supplements:
In vitro and in vivo research suggests that celery can inhibit cytochrome P450 1A2 (CYP1A2).[135] Theoretically concomitant use may increase the levels of CYP1A2 substrates. Some drugs metabolized by CYP1A2 include amitriptyline (Elavil), haloperidol (Haldol), ondansetron (Zofran), propranolol (Inderal), theophylline (Theo-Dur, others), verapamil (Calan, Isoptin, others), and others. Celery seed may decrease the effects of levothyroxine replacement therapy [136] when taken together. Celery is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, celery might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

Celery contains the constituents falcarinol and falcarindiol. Laboratory research suggests that falcarinol and falcarindiol can inhibit platelet aggregation [134] [137]
Anecdotal evidence suggests that celery can decrease blood pressure.[138] Theoretically, concomitant use with herbs with hypotensive effects might have additive blood pressure lowering effects and increase the risk of hypotension; use with caution. Some of these herbs include andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lycium, stinging nettle, theanine, and others.

Celery tuber also contains methoxsalen (8-methoxypsoralen) and 5-methoxypsoralen and the allergen profilin (Api g 1), which shows high homology to birch pollen profiling, and thus can cross react with those who are allergic to birch pollen.

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