PILOT STUDY

Five Herbs Plus Thiamine Reduce Pain and Improve Functional Mobility in Patients With Pain: A Pilot Study

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ABSTRACT

Context • Five herbs—*Urtica dioica* (stinging nettle), *Boswellia serrata*, *Equisetum arvense*, *Allium sativum*, and *Apium graveolens*—have been demonstrated to have activity at several anti-inflammatory pathways and have analgesic properties that are effective in treating chronic musculoskeletal pain.

Objectives • The study intended to evaluate the clinical efficacy of a proprietary blend of *U dioica*, *B serrata*, *E arvense*, *A sativum*, *A graveolens*, and thiamine (vitamin B_1), or "the blend," in the treatment of chronic musculoskeletal pain.

Methods • The research team performed a prospective case study.

Setting • The study took place at the National Center for Whole Psychiatry in Chevy Chase, MD, USA.

Participants: Participants were patients who had experienced baseline persistent musculoskeletal pain for at least 4 mo in ≥1 body parts without relief from traditional treatments.

Intervention • Participants were provided with a 14-d supply of the study's medication. Two 350-mg capsules were administered 2 ×/d with food. The participants were instructed not to alter or add any therapies for their pain-associated condition for the 14 d of the study.

Outcome Measures • The primary outcome measure was the change on a subjectively scored visual analogue scale (VAS), similar to the Western Ontario and McMaster Universities Osteoarthritis Index. The VAS was used to assess pain and the impact of motion and mobility at each location with pain. Each patient was administered the VAS rating scale to assess physical function and pain status at baseline and at the end of 14 d or postintervention. Patients were seen for follow-up at a minimum of 2 wk and underwent an interview, with the VAS rating scale being readministered.

Results • A total of 13 patients, involving 27 pain sites, qualified for the study, 5 males and 8 females with a median age of 58 y. The primary sites of pain were (1) the knees—5 sites (18.5%), (2) the shoulders—6 sites (16.6%), and (3) the back (sciatica)—5 sites (18.5%), with 11 miscellaneous locations (40.7%) making up the rest of the sites, including the neck, jaw, foot, heel, and coccyx. The mean disease duration was 5.61 y, with a range of 4 mo to 20 y. The average VAS pain subscale score was 58.04 at baseline and 23.33 at follow-up. The mean difference between the 2 scores was 34.71 (confidence interval [CI], 26.16–47.01). A significant reduction in the pain scores had occurred by the follow-up assessment ($t = 7.23$, $P < .05$). The average VAS subscale score for functional mobility was 56.67 at baseline and 28.70 at follow-up. The mean difference between the 2 mobility scores was 27.97 (CI, 17.86–38.88). A significant improvement in the ability to move had occurred in the affected areas by the follow-up assessment ($t = 5.97$, $P < .05$). No adverse effects were reported.

Conclusions • A clinically significant reduction in perceived pain and improvement in functional mobility had occurred for the intervention group as related to their chronic joint, back, and muscle pain. The complex of 5 herbs, plus vitamin B_1, was well tolerated, and the results suggest that the blend should be considered to be a valuable alternative treatment in the management of chronic musculoskeletal pain. (*Altern Ther Health Med.* 2017;23(1):14-19.)

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Chronic pain is a predominant manifestation of disease that results 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] Such pain is frequently refractory to treatment, and its prevalence continues to increase, with epidemiological studies reporting that up to 20% of those with chronic pain are refractory to standard, traditional therapies such as nonprescription analgesics, or prescription COX inhibitors and opioids.[2] It is estimated that those conditions result in $60 billion in lost productivity each year and will likely increase as individuals live longer and survive with medical conditions that are treatable.[3]

The World Health Organization reports that of those individuals with chronic pain, 50% identify the limbs and joints and 33% the lower back as the source of pain.[4] Joint and back pain is most commonly caused by arthritic conditions and is typically managed according to the guidelines of the American College of Rheumatology,[5] the 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, the side effects and risks are significant. Up to 50% of patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids experience gastrointestinal side effects.[7] Opioid treatments are associated with frequent adverse effects, including abuse, mental impairment, tolerance, nausea, and constipation, resulting in more than 20% of users discontinuing the medication[8] and approximately 40% being nonadherent to a physician's recommended dose.[9]

Alternative therapies, such as acupuncture and massage, have become widely used by patients when traditional medical treatments for chronic pain are not effective, medically contraindicated, poorly tolerated, or simply refused.[10] The traditional herbs *Urtica dioica*, *Boswellia serrata*, *Equisetum arvense*, *Allium sativum*, and *Apium graveolens* have been demonstrated to have activity at several anti-inflammatory pathways.

U dioica (stinging nettle) has been shown to be clinically effective in the treatment of arthritis.[11,12] *Boswellia* has been shown to be effective in reducing pain from osteoarthritis,[13-15] surgical tendon repair,[16] and repetitive-use arthritis,[17] as well as in human mechanical pain models.[18] *E arvense* reduces inflammation, produces antinociceptive actions,[19,20] and has been shown to reduce neuronal pain transmission signals.[19] *A sativum* bulb powder has specifically been shown to have analgesic effects in animal pain models.[21] *A graveolens* extracts reduce inflammation and improve arthritic conditions.[22] The family of B vitamins is essential for proper nerve-cell function, and combinations of vitamins B_1, B_6, and B_{12} have been reported to have analgesic effects and reduce pain associated with lumbar vertebral disease,[23] back pain,[24] and diabetic neuropathy.[25]

Urtica dioica

The proposed benefits of *U dioica* in the treatment of pain and inflammation may be due to components found in the extract of the leaf. In 2 studies, a fraction of an aqueous extract containing polysaccharides demonstrated prolonged anti-inflammatory activity in a rat-paw edema test.[26,27] Specific polysaccharides isolated from that fraction stimulated T-lymphocyte proliferation or influenced the complement system. An ethanolic extract was found to 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.[28]

The water-soluble fraction of stinging-nettle leaf extract (IDS 23, Rheuma-Hek, Strathmann GmbH & Co KG, Hamburg, Germany) was shown to provide a dose-dependent inhibition of a phytohemagglutinin-stimulated production of T-helper type 1 (Th_1)-specific interleukin (IL) 2 and of interferon-gamma in peripheral-blood mononuclear cells.[29] It has been demonstrated to inhibit the action of leukotriene and prostaglandin syntheses,[30] reduce the formation of tumor necrosis factor α (TNF-α), influence T-helper-derived cytokine patterns,[29] reduce the stimulation of IL-1β in lipopolysaccharide-stimulated human whole blood,[30] and inhibit the action of nuclear factor κB (NF-κB).[11] A hydroalcoholic extract of stinging nettle was found to lower levels of IL-6 and high-sensitivity C-reactive protein (hs-CRP), but it lacked significant effects on TNF-α.[31]

Stinging nettle has been used safely for up to 2 years.[32] Stinging nettle root extract (Bazoton-uno) was shown to be safe and effective in a randomized, controlled, long-term study of benign prostatic syndrome.[33]

Boswellia

Multiple pentacyclic triterpenic acids, referred to as *boswellic acids*, have been isolated from resins of the *Boswellia* species and identified as possessing anti-inflammatory properties.[34] Acetyl-11-keto-β boswellic acid from *Boswellia* has been identified as one of the primary anti-inflammatory triterpenoid acids in *Boswellia* resin extract. Acetyl-11-β boswellic acid is a highly specific inhibitor of 5-lipoxygenase, an enzyme for leukotriene biosynthesis.[35,36] Animal research has shown that it inhibits the release of leukotrienes B_4 (LTB_4).[34,37,38] Additional studies have found that *Boswellia* inhibits HLE.[39]

For mice with colitis induced by trinitrobenzene sulfonic acid, high doses of *Boswellia* extracts were found to be effective at reducing inflammatory responses. In a randomized, double-blind, placebo-controlled, crossover trial of 30 patients, the safety and efficacy of *B serrata* for individuals with osteoarthritis of the knee was studied.[40] The findings revealed a statistical reduction in pain and improved function of the affected joint and limb.

Equisetum arvense

E telmateia contains antioxidants with significant inhibitory actions against damaging free-radicals.[41] *E arvense* also contains β-sitosterol, campesterol, and isofucosterol, which provide anti-inflammatory steroidal effects.[42]

Allium sativum

The pharmacological effects of *A sativum* (garlic) are attributed to its allicin, ajoene, and *S*-allyl-L-cysteine sulfoxide (ACSO).[43] Specifically, ACSO possesses significant antioxidant and anti-inflammatory properties. Recent research has demonstrated that ACSO can reduce mitochondrial production of proinflammatory superoxide anions and harmful cellular activations of cytokines.[44]

Allicin supplementation has been studied to examine the effects of exercise induced muscle damage.[45] That study found that allicin supplementation for 14 days reduced plasma creatine kinase, muscle-specific creatine kinase, and IL-6 as well as decreased subjectively assessed muscle soreness after exercise. That study's allicin supplementation resulted in reduced, exercise-induced plasma creatine kinase, muscle-specific creatine kinase, IL-6, and perceived muscle soreness after exercise when compared with a placebo. No adverse effects were reported.

Apium graveolens

One study has shown that *A graveolens* from celery contains flavone aglycones, which can inhibit 2 proinflammatory mediators, TNF-α, and NF-κB.[46] The objective of that study was to assess the efficacy, safety, and tolerability of *A graveolens* for the treatment of patients with chronic musculoskeletal pain.

METHODS

Participants

The participants in the current study were a series of consecutive patients presenting with pain at the author's clinic, the National Center for Whole Psychiatry (Chevy Chase, MD, USA).

To qualify for inclusion in the current prospective analysis, a patient must have experienced baseline persistent musculoskeletal pain for at least 4 months in 1 or more locations on the body without adequate relief. A review of a prospective participant records by the author determined if he or she met the criteria for enrollment. To be included, the patient must (1) have been older than 18 years, (2) not have been lactating or pregnant, and (3) have had musculoskeletal pain for more than 4 months.

Patients on anticoagulant therapy were excluded from the study because the investigator was concerned that stinging nettle, which contains significant amounts of vitamin K, might decrease the effects of anticoagulant drugs such as warfarin (Coumadin).[47] Patients with gastrointestinal disorders were excluded based on the results of a randomized controlled trial in which 4 of 25 patients treated with a stinging-nettle preparation withdrew from the study owing to side effects such as constipation, diarrhea, and gastric disorder.[48]

Procedures

The research team performed a prospective case study, which intended to evaluate the clinical efficacy of a proprietary blend of *U dioica*, *B serrata*, *E arvense*, *A sativum*, *A graveolens*, and vitamin B_1 (DrH Rejoint Functional Herbals, LLC, Chevy Chase, MD, USA) in the treatment of chronic musculoskeletal pain.

Each patient subjectively completed a visual analogue scale (VAS) similar to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index to assess physical function and pain status at baseline and postintervention. The effectiveness of the blend was evaluated on treatment day 14, by comparing the VAS data postintervention to the baseline values. The primary outcome measure was the change on the VAS, which was measured for each location of pain. The effects of pain on the range of motion (ROM) in the patient's affected body region and on mobility was also assessed.

The patients were seen for follow-up at 2 weeks postintervention and underwent an interview, with the VAS rating scale being readministered. In cases where the patient was unable to return to the clinic for follow-up, a VAS was mailed to the patient. The investigators collected symptom reports at the posttreatment measurement that included an assessment of side effects and adverse events.

During the study, the participants were instructed not to change the type or dosage of medications or to begin any new therapies for their chronic pain condition during the study. They were authorized to continue any previously ongoing therapies related to their general health as well as to their chronic pain. Those ongoing therapies consisted of psychotropic medications, counseling, prescription analgesic medications, an anti-inflammatory diet, various nutritional supplements, and meditation.

Intervention

All patients took two 350-mg capsules of the blend with food twice per day. Participants were provided with a 14-day supply of the study's medication.

Outcome Measures

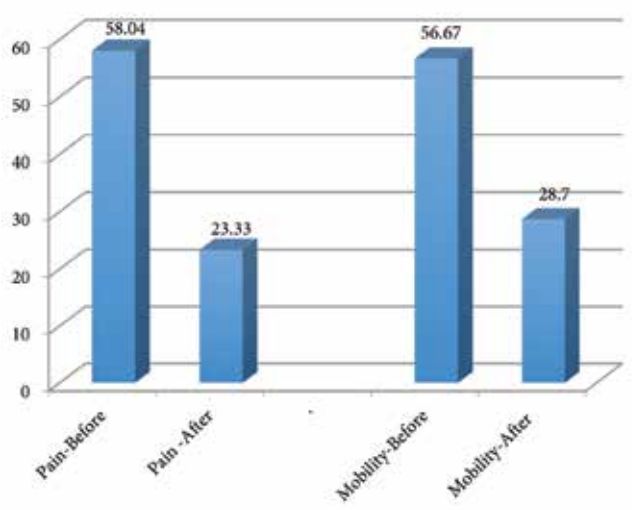
The VAS used was similar in design to the WOMAC Index.[49-51] The VAS consisted of subscales for pain and functional mobility, which provided parallel, 60 mm-long horizontal lines labeled *pain* and *trouble moving the painful area*, respectively. Each line was marked from 0 to 100, divided into 10 segments, and associated with a descriptive word at each end (ie, *none* at one end and *worst ever* at the other).

The patients marked the point on the line that best reflected the place on the scale that described their current pain and immobility. The measurement between zero and the point marked by a patient was compiled as a percentage of the line's total length and entered into the study's data sheet for compilation and computation.

Statistical Analyses

The individual scores were analyzed by an analysis of variance with calculated statistical *t* scores and *P* values.

Figure 1. VAS Scores at Baseline and Postintervention



Abbreviations: VAS, visual analogue scale.

RESULTS

A total of 13 patients, involving 27 pain sites, qualified for the study. The study included 5 males and 8 females, with a median age of 58 years and a range of 48 to 75 years. The primary sites of pain were the (1) knees—5 sites (18.5%), (2) shoulders—6 sites (16.6%), and (3) back (sciatica)—5 sites (18.5%), with 11 miscellaneous locations (40.7%) making up the rest of the sites, including the neck, jaw, foot, heel, and coccyx.

The mean disease duration was 5.61 years, with a range from 4 months to 20 years. The average VAS subscale score for pain was 58.04 mm at baseline and decreased to 23.33 mm at follow-up. At the endpoint, the mean difference between the 2 scores was 34.71 mm (confidence interval [CI], 26.16–47.01). A significant reduction in the VAS pain scores was found at a follow-up assessment ($t = 7.23$, $P < .05$). The average VAS subscale score for functional mobility was 56.67 at baseline and 28.70 at follow-up. At the endpoint, the mean difference between the 2 scores was 27.97 (CI, 17.86–38.88). A significant improvement was found in the patients' ability to move the affected joints at the follow-up assessment ($t = 5.97$, $P < .05$). See Figure 1. The mean reduction in the pain score was 59.9% and the reduction in the limitations on mobility was 49.4%. No adverse effects were reported.

DISCUSSION

The current study was designed to determine whether administration of a proprietary blend of *U dioica*, *B serrata*, *E arvense*, *A sativum*, *A graveolens*, and vitamin B_1 would result in significant subjective improvements in patients with chronic musculoskeletal pain. The study did in fact demonstrate a significant reduction in pain and improvements in functional mobility. More important, the mean reduction in pain scores in the study was greater than many average scores for placebo effects that have been reported in clinical analgesia trials.[52,53] Assessing the ROM was not an objective of the current study and, therefore, was not measured for the study's patients.

The secondary objective of the current study was to assess any change in the pain associated with the movement of the affected region of the body—shoulder, knee, back, or other area—that contributed to limiting a patient's ROM and/or mobility. The study found that improved mobility was a likely result because of a reduction in the pain associated with the movement of the affected regions. Thus, the current pilot study confirmed the researcher's hypothesis that the herbal blend would have analgesic and/or anti-inflammatory properties that were associated with improvement in chronic musculoskeletal pain and mobility.

The herbs in the blend have numerous biologically active constituents, which act at multiple locations along inflammatory and nociceptive pathways. *Boswellia* has significant antioxidant properties and may act by limiting the proinflammatory effects of free-radical excess, which are both consequences and causes of chronic tissue injury.[54] *Boswellia* reduces leukocyte infiltration in arthritic joints and reduces inflammation by inhibiting NK-κB.[55]

U dioica has been shown to be clinically effective in the treatment of arthritis, and it is thought that its strong anti-inflammatory action is the result of stabilization of the NF-κB complex.[56] In addition, *U dioica* is associated with inhibition of cytosolic phospholipase $A_{2\alpha}$[57] and also has antioxidant properties.[58,59]

E arvense has been shown in animal models to have strong antinociceptive and anti-inflammatory properties[19] and an inhibitory effect on human T-cell proliferation, which subsequently limits inflammatory processes.[60] In addition, *E arvense* induces antinociceptive actions that are achieved by a reduction of IL-2 and TNF-α activity.[60]

A graveolens has been shown to provide antioxidative,[61,62] central analgesic, and local-tissue anti-inflammatory action[63-65] via inhibition of TNF-α and NF-κB.[66] *A sativum* has been shown to reduce proinflammatory cytokines, IL-1, and IL-6[67-70] and to minimize intracellular oxidative stress and NF-κB activation.[71,72]

Vitamin B_1 is an important cofactor in the biosynthesis of both neurotransmitters and reducing substances that prevent cellular oxidative damage.[73] The analgesic effects of vitamin B_1 have been studied in several human clinical trials, and benefits have been found in the treatment of peripheral neuropathies as well as fibromyalgia.[74]

The current researcher concludes that the proprietary blend was effective in patients with chronic musculoskeletal pain and is a reasonable alternative for those individuals who prefer nonpharmacological pain management; are nonresponders to existing treatments; have renal or cardiovascular risk factors precluding NSAID use; or cannot tolerate NSAIDs, COX-2 inhibitors, or opioids.

The limitations of the current study are the relatively small sample size, lack of a randomly assigned placebo arm, and use of subjective assessments. Although measures of

pain are generally subjective, future studies should use objective measures for range of motion. Finally, the study's duration was limited, and it will be important to determine how or whether the subjective benefits of the blend change over time. Based on those limitations, it is clear that additional studies are necessary to confirm the efficacy and safety of the blend in patients with chronic musculoskeletal pain.

CONCLUSIONS

The study found significant improvements in the levels of pain and functional mobility for patients administered a proprietary blend for chronic musculoskeletal pain. Based on its significant clinical effects, its excellent tolerance profile, and the broad spectrum of its molecular anti-inflammatory actions, the blend appears to be a valuable alternative to NSAIDs, COX-2 inhibitors, and opioids in patients suffering from refractory chronic musculoskeletal pain.

AUTHOR DISCLOSURE STATEMENT

Robert Hedaya is the chief executive officer of Functional Herbals and Old Chester Health Care Products, LLC, the makers of the blend used in the current study.

REFERENCES

1. Lamerato LE, Dryer RD, Wolff GG, et al. Prevalence of chronic pain in a large integrated healthcare delivery system in the U.S.A. *Pain Pract. 2016;16(7):890-898.*
2. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain.* 2006;10(4):287-333.
3. Krueger AB, Stone AA. Assessment of pain: a community-based diary survey in the USA. *Lancet,* 2008;371(9623):1519-1525.
4. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bull World Health Organ.* 2003;81(9):646-656.
5. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis Rheum.* 2000;43(9):1905-1915.
6. Chou R, Qaseem A, Snow V, et al. Diagnosis and treatment of low back pain: A joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med.* 2007;147(7): 478-491.
7. Lanas A, Tornero J, Zamorano JL. Assessment of gastrointestinal and cardiovascular risk in patients with osteoarthritis who require NSAIDs: The LOGICA study. *Ann Rheum Dis.* 2010;69(8):1453-1458.
8. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: Systematic review of randomised trials of oral opioids. *Arthritis Res Ther.* 2005;7(5):R1046-R1051.
9. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: A systematic review. *Acta Anaesthesiol Scand. 2016;60(4):416-431.*
10. Gore M, Tai KS, Sadosky A, Leslie D, Stacey BR. Use and costs of prescription medications and alternative treatments in patients with osteoarthritis and chronic low back pain in community-based settings. *Pain Pract.* 2012;12(7):550-560.
11. Riehemann K, Behnke B, Schulze-Osthoff K. Plant extracts from stinging nettle (Urtica dioica), an antirheumatic remedy, inhibit the proinflammatory transcription factor NF-kappaB. *FEBS Lett.* 1999;442(1): 89-94.
12. Randall C, Randall H, Dobbs F, Hutton C, Sanders H. Randomized controlled trial of nettle sting for treatment of base-of-thumb pain. *J R Soc Med.* 2000;93(6):305-309.
13. Grover AK, Samson SE. Benefits of antioxidant supplements for knee osteoarthritis: Rationale and reality. *Nutr J.* 2016;15(1):1.
14. Belcaro G, Dugall M, Luzzi R, Ledda A, Pellegrini L, Hu S, Ippolito E. Management of osteoarthritis (OA) with the pharma-standard supplement FlexiQule (Boswellia): A 12-week registry. *Minerva Gastroenterol Dietol. October 2015. [Epub ahead of print]*
15. Di Lorenzo C, Dell'Agli M, Badea M, et al. Plant food supplements with anti-inflammatory properties: A systematic review (II). *Crit Rev Food Sci Nutr.* 2013;53(5):507-516.
16. Merolla G, Dellabiancia F, Ingardia A, Paladini P, Porcellini G. Co-analgesic therapy for arthroscopic supraspinatus tendon repair pain using a dietary supplement containing Boswellia serrata and Curcuma longa: A prospective randomized placebo-controlled study. *Musculoskelet Surg.* 2015;99(Suppl 1):S43-S52.
17. Belcaro G, Feragalli B, Cornelli U, Dugall M. Hand 'stress' arthritis in young subjects: effects of Flexiqule (pharma-standard Boswellia extract): A preliminary case report. *Minerva Gastroenterol Dietol.* October *2015. [Epub ahead of print]*
18. Prabhavathi K, Chandra US, Soanker R, Rani PU. A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of Boswellia serrata in healthy volunteers using mechanical pain model. *Indian J Pharmacol.* 2014;46(5):475-479.
19. Do Monte FH, dos Santos JG Jr, Russi M, Lanziotti VM, Leal LK, Cunha GM. Antinociceptive and anti-inflammatory properties of the hydroalcoholic extract of stems from Equisetum arvense L. in mice. *Pharmacol Res.* 2004;49(3):239-243.
20. Asgharikhatooni A, Bani S, Hasanpoor S, Mohammad Alizade S, Javadzadeh Y. The effect of equisetum arvense (horse tail) ointment on wound healing and pain intensity after episiotomy: A randomized placebo-controlled trial. *Iran Red Crescent Med J.* 2015;17(3):e25637.
21. Jayanthi MK, Jyoti M. Experimental animal studies on analgesic and anti-nociceptive activity of Allium sativum (Garlic) powder. *IJRRMS.* 2012;2(1):1-6.
22. Powanda MC, Whitehouse MW, Rainsford KD. Celery seed and related extracts with antiarthritic, antiulcer, and antimicrobial activities. *Prog Drug Res.* 2015;70:133-153.
23. Bruggemann G, Koehler CO, Koch EM. Results of a double-blind study of diclofenac + vitamin B1, B6, B12 versus diclofenac in patients with acute pain of the lumbar vertebrae. A multicenter study. *Klin Wochenschr.* 1990;68(2):116-120.
24. Mauro GL, Martorana U, Cataldo P, Brancato G, Letizia G. Vitamin B12 in low back pain: A randomised, double-blind, placebo-controlled study. *Eur Rev Med Pharmacol Sci.* 2000;4(3):53-58.
25. Abbas ZG, Swai AB. Evaluation of the efficacy of thiamine and pyridoxine in the treatment of symptomatic diabetic peripheral neuropathy. *East Afr Med J.* 1997;74(12):803-808.
26. Bombardelli E, Morazzon P. Urtica dioica L. *Fitoterapia.* 1997;68:387-402.
27. Wagner H, Willer F, Samtleben R, Boos G. Search for the antiprostatic principle of stinging nettle (Urtica dioica) roots. *Phytomedicine.* 1994;1(3):213-224.
28. Koch E. Extracts from fruits of saw palmetto (Sabal serrulata) and roots of stinging nettle (Urtica dioica): Viable alternatives in the medical treatment of benign prostatic hyperplasia and associated lower urinary tracts symptoms. *Planta Med.* 2001;67(6):489-500.
29. Klingelhoefer S, Obertreis B, Quast S, Behnke B. Antirheumatic effect of IDS 23, a stinging nettle leaf extract, on in vitro expression of T helper cytokines. *J Rheumatol.* 1999;26(12):2517-2522.
30. Obertreis B. Anti-inflammatory effect of Urtica dioica folia extract in comparison to caffeic malic acid. *Arzneimittelforschung.* 1996;46(1):52-56.
31. Namazi N, Esfanjani AT, Heshmati J, Bahrami A. The effect of hydro alcoholic Nettle (Urtica dioica) extracts on insulin sensitivity and some inflammatory indicators in patients with type 2 diabetes: A randomized double-blind control trial. *Pak J Biol Sci.* 2011;14(15):775-759.
32. Lopatkin N, Sivkov A, Walther C, et al. Long-term efficacy and safety of a combination of sabal and urtica extract for lower urinary tract symptoms: A placebo-controlled, double-blind, multicenter trial. *World J Urol.* 2005;23(2):139-146.
33. Schneider T, Rubben H. Stinging nettle root extract (Bazoton-uno) in long term treatment of benign prostatic syndrome (BPS): Results of a randomized, double-blind, placebo controlled multicenter study after 12 months. *Urologe A.* 2004;43(3):302-306.
34. Ammon HP. Boswellic acids in chronic inflammatory diseases. *Planta Med.* 2006;72(12):1100-1116.
35. Safayhi H, Sailer ER, Ammon HP. Mechanism of 5-lipoxygenase inhibition by acetyl-11-keto-beta-boswellic acid. *Mol Pharmacol.* 1995;47(6):1212-1216.
36. Sailer ER. Acetyl-11-keto-beta-boswellic acid (AKBA): Structure requirements for binding and 5-lipoxygenase inhibitory activity. *Br J Pharmacol.* 1996;117(4):615-618.
37. Ammon HP. Salai Guggal - Boswellia serrata: From an herbal medicine to a non-redox inhibitor of leukotriene biosynthesis. *Eur J Med Res.* 1996;1(8):369-370.
38. Ammon HP, Safayhi H, Mack T, Sabieraj J. Mechanism of antiinflammatory actions of curcumine and boswellic acids. *J Ethnopharmacol.* 1993;38(2-3):113-119.
39. Kiela PR, Midura AJ, Kuscuoglu N, et al. Effects of Boswellia serrata in mouse models of chemically induced colitis. *Am J Physiol Gastrointest Liver Physiol.* 2005;288(4):G798-G808.
40. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee: A randomized double blind placebo controlled trial. *Phytomedicine.* 2003;10(1):3-7.
41. Stajner D, Popović BM, Canadanović-Brunet J, Boza P. Free radical scavenging activity of three Equisetum species from Fruska gora mountain. *Fitoterapia.* 2006;77(7-8):601-604.
42. D'Agostino M. Sterols from Equisetum arvense. *Boll Soc Ital Biol Sper.* 1984;60(12):2241-2245.
43. Ali M, Thomson M, Afzal M. Garlic and onions: Their effect on eicosanoid metabolism and its clinical relevance. *Prostaglandins Leukot Essent Fatty Acids.* 2000;62(2):55-73.
44. Hui C. S-allyl-L-cysteine sulfoxide inhibits tumor necrosis factor-alpha induced monocyte adhesion and intercellular cell adhesion molecule-1 expression in human umbilical vein endothelial cells. *Anat Rec (Hoboken).* 2010;293(3):421-430.
45. Su QS, Tian Y, Zhang JG, Zhang H. Effects of allicin supplementation on plasma markers of exercise-induced muscle damage, IL-6 and antioxidant capacity. *Eur J Appl Physiol.* 2008;103(3):275-283.
46. Hostetler G, Riedl K, Cardenas H, et al. Flavone deglycosylation increases their anti-inflammatory activity and absorption. *Mol Nutr Food Res.* 2012;56(4):558-569.
47. Brinker F. *Herb Contraindications and Drug Interactions.* 2nd ed. Sandy, Oregon: Eclectic Medical Publications; 1998.

48. Vontobel HP. Results of a double-blind study on the effectiveness of ERU (extractum radicis Urticae) capsules in conservative treatment of benign prostatic hyperplasia. *Urologe A*. 1985;24(1):49-51.
49. Bellamy N. *WOMAC Osteoarthritis Index User Guide, in Version V*. Brisbane, Queensland, Australia; 2002.
50. McConnell S, Kolopack P, Davis AM. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): A review of its utility and measurement properties. *Arthritis Rheum*. 2001;45(5):453-461.
51. Angst F. The factor subdimensions of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) help to specify hip and knee osteoarthritis. a prospective evaluation and validation study. *J Rheumatol*. 2005;32(7):1324-1330.
52. Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*. 2002;99(3):443-452.
53. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med*. 2001;344(21):1594-1602.
54. Mothana RA. Anti-inflammatory, antinociceptive and antioxidant activities of the endemic Soqotraen Boswellia elongata Balf. f. and Jatropha unicostata Balf. f. in different experimental models. *Food Chem Toxicol*. 2011;49(10):2594-2599.
55. Takada Y, Ichikawa H, Badmaev V, Aggarwal BB. Acetyl-11-keto-beta-boswellic acid potentiates apoptosis, inhibits invasion, and abolishes osteoclastogenesis by suppressing NF-kappa B and NF-kappa B-regulated gene expression. *J Immunol*. 2006;176(5):3127-3140.
56. Dar SA, Ganai FA, Yousuf AR, Balkhi MU, Bhat TM, Sharma P. Pharmacological and toxicological evaluation of Urtica dioica. *Pharm Bio*. 2013;51(2):170-180.
57. Arnold E, Benz T, Zapp C, Wink M. Inhibition of cytosolic phospholipase A2alpha (cPLA2alpha) by medicinal plants in relation to their phenolic content. *Molecules*. 2015;20(8):15033-15048.
58. Gulcin I, Küfrevioglu OI, Oktay M, Büyükokuroglu ME. Antioxidant, antimicrobial, antiulcer and analgesic activities of nettle (Urtica dioica L.). *J Ethnopharmacol*. 2004;90(2-3): 205-215.
59. Mavi A, Terzi Z, Ozgen U, Yildirim A, Coşkun M. Antioxidant properties of some medicinal plants: Prangos ferulacea (Apiaceae), Sedum sempervivoides (Crassulaceae), Malva neglecta (Malvaceae), Cruciata taurica (Rubiaceae), Rosa pimpinellifolia (Rosaceae), Galium verum subsp. verum (Rubiaceae), Urtica dioica (Urticaceae). *Biol Pharm Bull*. 2004;27(5):702-705.
60. Grundemann C, Lengen K, Sauer B, Garcia-Käufer M, Zehl M, Huber R. Equisetum arvense (common horsetail) modulates the function of inflammatory immunocompetent cells. *BMC Complement Altern Med. August 2014;14:283.*
61. Popovic M, Kaurinović B, Trivić S, Mimica-Dukić N, Bursać M. Effect of celery (Apium graveolens) extracts on some biochemical parameters of oxidative stress in mice treated with carbon tetrachloride. *Phytother Res*. 2006;20(7):531-537.
62. Momin RA, Nair MG. Antioxidant, cyclooxygenase and topoisomerase inhibitory compounds from Apium graveolens Linn. seeds. *Phytomedicine*. 2002;9(4):312-318.
63. Ramezani M. Antinociceptive and anti-inflammatory effects of isolated fractions from Apium graveolens seeds in mice. *Pharmaceutical Biology*. 2009;47(8):740-743.
64. Atta AH, Alkofahi A. Anti-nociceptive and anti-inflammatory effects of some Jordanian medicinal plant extracts. *J Ethnopharmacol*. 1998;60(2):117-124.
65. Al-Hindawi MK, Al-Deen IH, Nabi MH, Ismail MA. Anti-inflammatory activity of some Iraqi plants using intact rats. *J Ethnopharmacol*. 1989;26(2):163-168.
66. Si Y, Guo S, Fang Y. Celery seed extract blocks peroxide injury in macrophages via Notch1/NF-kappaB pathway. *Am J Chin Med*. 2015;43(3):443-455.
67. Yun HM, Ban JO, Park KR, et al. Potential therapeutic effects of functionally active compounds isolated from garlic. *Pharmacol Ther*. 2014;142(2):183-195.
68. Lee da Y, Li H, Lim HJ, Lee HJ, Jeon R, Ryu JH. Anti-inflammatory activity of sulfur-containing compounds from garlic. *J Med Food*. 2012;15(11):992-999.
69. Lee SH, Liu YT, Chen KM, Lii CK, Liu CT. Effect of garlic sulfur compounds on neutrophil infiltration and damage to the intestinal mucosa by endotoxin in rats. *Food Chem Toxicol*. 2012;50(3-4):567-574.
70. Keiss HP, Dirsch VM, Hartung T, et al. Garlic (Allium sativum L.) modulates cytokine expression in lipopolysaccharide-activated human blood thereby inhibiting NF-kappaB activity. *J Nutr*. 2003;133(7):2171-2175.
71. Ide N, Lau BH. Garlic compounds minimize intracellular oxidative stress and inhibit nuclear factor-kappa b activation. *J Nutr*. 2001;131(3s):1020S-1026S.
72. Ryu K. N alpha-(1-deoxy-D-fructos-1-yl)-L-arginine, an antioxidant compound identified in aged garlic extract. *J Nutr*. 2001;131(3s): 972S-976S.
73. Fattal-Valevski A. Thiamine (vitamin B1). *J Evidence-Based Complement Altern Med*. 2011;16(1):12-20.
74. Costantini A, Pala MI, Tundo S, Matteucci P. High-dose thiamine improves the symptoms of fibromyalgia. *BMJ Case Rep. May* 2013;2013:pii: bcr2013009019.