SYSTEMATIC REVIEW

ANTIOXIDANTS AND ANTIINFLAMMATORY DIETARY SUPPLEMENTS FOR OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

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Objective • To review efficacy studies of antioxidant and antiinflammatory dietary supplements used to manage osteoarthritis (OA) and rheumatoid arthritis (RA) and make conclusions about their place in therapy. Glucosamine, chondroitin, and methyl sulfonyl methane were excluded.

Data Sources • A literature search was conducted using MEDLINE (1996 through January 2009), EMBASE, Cochrane Library, Natural Medicines Comprehensive Database, and Natural Standard, with bibliographic review of relevant articles. Cited studies from before our search range were included if they represented the only published human data available. Search words included "antioxidant," "antiinflammatory," "cat's claw," "ginger," "fish oil," "omega-3," "turmeric," "vitamin E," "vitamin C," "Baikal skullcap," "barberry," "Chinese goldthread," "green tea," "Indian holy basil," "hu zhang," "oregano," and "rosemary."

Study Selection and Data Extraction • Efficacy studies published in English were included provided they evaluated the dietary supplements in patients with OA or RA.

Data Synthesis • Our search strategy yielded 16 clinical studies (11 randomized, placebo-controlled clinical trials, three crossover trials, one case-controlled study, and one open-label study) in addition to one meta-analysis and one review article.

Conclusions • Three studies support cat's claw alone or in combination for OA, and two studies support omega-3 fatty acids for the treatment of RA. We cannot recommend use of vitamin E alone; vitamins A, C, and E in combination; ginger; turmeric; or Zyflamend (New Chapter, Brattleboro, Vermont) for the treatment of OA or RA or omega-3 fatty acids for OA. Whether any of these supplements can be effectively and safely recommended to reduce nonsteroidal antiinflammatory drug or steroid usage is unclear and requires more high-quality research. (*Altern Ther Health Med.* 2010;16(2):32-40.)

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The term *arthritis* refers to multiple diseases and conditions affecting joints and joint function. Arthritis is among the most common causes of chronic disability in the United States. Osteoarthritis (OA) affects approximately 15% of the US population.[1] Total arthritis-related medical costs (including hospitalization) are estimated to be in excess of $125 billion USD annually.[2] Current management of rheumatoid arthritis (RA) and OA includes exercise, weight reduction, and nonpharmacological and pharmacological therapies. New guidelines from the American College of Rheumatology for the treatment of patients with RA have been published.[3] Pharmacological therapies, although often effective, may be associated with serious long-term adverse effects.

In OA, persistent stress on joint tissues leads to inflammation. Mechanical stress leads to increased production of cytokines and growth factors that induce progression and/or initiation of OA.[4] Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthases (iNOS) are responsible for increased production of prostaglandins (PGs) and leukotrienes (LTs), specifically PGE_2 and LTB_4.[5] Tumor necrosis factor–alpha (TNF-α) and nuclear factor–kappa beta (NF-κβ) are excessively active in OA and RA.

OA is no longer considered merely a wear-and-tear phenomenon. Obesity in humans has been shown to stress joints, increase risk of OA, and promote a chronic proinflammatory state associated with increased plasma concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), and plasminogen activator inhibitor (PAI-1).[6] Chronic overnutrition with excessive glucose and caloric intake may cause oxidative stress, inhibiting

some of these markers. Increased concentrations of TNF-α and IL-6 associated with obesity, insulin resistance, and type 2 diabetes may impede insulin activity by suppressing insulin signal transduction. This impedance is thought to cause inflammation.[7]

Reactive oxygen species (ROS) production is associated with damage to cartilage matrix components, by either direct or indirect attack, which reduces matrix components' synthesis. ROS appear to be components of OA-induced tissue injury since human chondrocytes can produce superoxide and hydrogen peroxide.[8,9]

RA is a chronic autoimmune inflammatory disorder involving genetic, immunological, and other changes characterized by progressive and painful synovitis, which manifests as polyarticular joint swelling.[10,11] RA mainly affects the small joints of the hands and feet with eventual erosion of cartilage and bone leading to deformity and destruction of these joints. Extraarticular manifestations such as vasculitis, nodules, sicca syndrome, and cardiac or lung involvement can develop, particularly in patients with severe disease.[12]

RA affects women two to three times more often than men, with the peak onset between the ages of 30 and 55 years. Once diagnosed, patients usually develop moderate disability within 2 years, and after 10 years, 50% of those afflicted are unable to work. Mortality rates are increased at least twofold.[13,14] RA results in more than 9 million physician visits and more than 250 000 hospitalizations in the United States annually.

The objective of this article is to review efficacy studies involving antioxidants and antiinflammatory agents used to manage OA and RA and make conclusions about their place in therapy. Regarding antioxidants, the use of vitamin E in OA and RA and the combination of vitamins E, C, and A in RA were reviewed. Regarding antiinflammatory agents, the use of ginger and omega-3 fatty acids were reviewed in OA, and omega-3 fatty acids were reviewed in RA. For combination antioxidant/antiinflammatory products in OA and RA, cat's claw, turmeric, and Zyflamend (New Chapter, Brattleboro, Vermont; constituents: Baikal skullcap, barberry, Chinese goldthread, ginger, green tea, Indian holy basil, hu zhang, oregano, rosemary, and turmeric) were reviewed. Because there are no human clinical trials with Zyflamend for the treatment of OA or RA, in vitro research for each of the 10 constituents is briefly reviewed, with the exception of one crossover study utilizing a combination of turmeric and boswellia in OA patients.

Other common arthritis products were excluded from this review if their mechanism of action was other than antioxidant or antiinflammatory. Thus, glucosamine (builds cartilage), chondroitin (adds fluid to joints and builds cartilage), methyl sulfonylmethane (MSM, antiinflammatory on muscle, not joints, and an analgesic), and flavocoxid, which is classed as a medical food, were excluded. For more information on the latter products, refer to the published literature.[15-21]

METHODOLOGY

Medline, EMBASE, the Cochrane Database, Natural Standard, and the Natural Medicines Comprehensive Database were searched from 1996 through January 2009. The search words used were "antioxidant," "antiinflammatory," "cat's claw," "ginger," "fish oil," "omega-3," "turmeric," "vitamin E," "vitamin C," "Baikal skullcap," "barberry," "Chinese goldthread," "green tea," "Indian holy basil," "hu zhang," "oregano," and "rosemary."

Citations were excluded if the studies were conducted in patients other than those with OA or RA or if they were published in a language other than English. Only efficacy studies with a control group were included. The bibliographies of all relevant articles were examined for additional efficacy studies. Cited studies from before our search range (prior to 1996) were included if they represented the only published human data available. This led to the inclusion of two turmeric studies.

A total of 16 studies met the inclusion criteria. These were 11 randomized placebo-controlled trials, three crossover trials, one case-control study, and one open-label study. The search strategy also revealed one meta-analysis and one review article that substantiated the clinical recommendations reached by this review for each agent.

Antioxidants: OA and RA Clinical Studies

Vitamin E (α-tocopherol)

People with antioxidant-deficient diets may have an increased risk of OA or RA.[22,23] A double-blind, placebo-controlled randomized trial comparing the effect of 500 IU of vitamin E daily with placebo on Western Ontario and McMaster Osteoarthritis Index (WOMAC) assessed pain, stiffness, and function in 77 patients with symptomatic knee OA.[24] WOMAC is a disease-specific, self-administered tool. Pain was assessed monthly during the 6-month study period. The placebo group had significantly higher body mass index (BMI) (30.5 compared to 27.6, P=.03) and higher pain levels at baseline. The study was powered to detect a 30% improvement in the three measured dimensions. The authors used a validated food frequency questionnaire to assess dietary vitamin E intake (no other antioxidants). Baseline and posttreatment serum antioxidant levels were not measured. No statistically significant improvements in pain, stiffness, or physical function occurred in either group over the study period. No differences remained after adjusting for baseline pain scores. The authors concluded that vitamin E is not effective in the treatment of knee OA.

Another double-blind, randomized, placebo-controlled trial evaluated the effect of 500 IU vitamin E daily in 136 patients with knee OA over 2 years.[25] The primary outcome measure was change in knee cartilage volume (measured by magnetic resonance imaging). A validated food frequency questionnaire was used to evaluate dietary antioxidant intake. Vitamin E did not alter articular cartilage volume. While both placebo and vitamin E groups experienced improvements in pain and stiffness WOMAC scores, the two groups did not differ significantly. This study was powered to detect a 50% change in cartilage loss. Baseline and posttreatment antioxidant blood values were not measured in either group. Once again, the authors concluded vitamin E is not effective in the treatment of knee OA.

A prospective placebo-controlled, double-blind randomized trial evaluated the effect of vitamin E on RA in 42 patients.[26] Patients in this study were maintained on standard treatment (including nonsteroidal antiinflammatory drugs [NSAIDs], disease-modifying antirheumatic drugs [DMARDs], and analgesic medications) and given either 1200 IU of d-α-tocopherol or placebo daily for 12 weeks to test for any additional analgesic and antiinflammatory effects. Results were evaluated using intent-to-treat analysis. Investigators measured clinical efficacy using the Ritchie Articular Index (RAI)[27] and early-morning stiffness (EMS) after 1, 4, 8, and 12 weeks of treatment. Dietary intake of vitamin E was not recorded. Baseline and posttreatment antioxidant blood levels were not reported. Both groups experienced a non–statistically significant reduction in RAI and EMS. In addition, vitamin E supplements did not reduce the use of NSAIDs or DMARDs in the treatment of RA.

Vitamins E, C, & A Combined

The effect of antioxidant supplementation was studied in a case control trial with 40 patients newly diagnosed with RA. Patients were divided into two groups; one (n=20) received standard treatment (NSAIDs and steroids) and the other (n=20) received standard treatment plus a fixed dose combination of the antioxidants vitamins A, E, and C. Twenty sex- and age-matched "normal individuals" served as controls.[28] Data were collected at baseline and after 12 weeks of treatment. The primary outcome was disease activity as measured by the Rheumatoid Arthritis Disease Activity (RADA) Index.[29] Total blood thiols, glutathione, vitamin C, and malondialdehyde (MDA-marker of oxidative stress) also were measured. The RADA Index showed significant decreases in disease state severity in both the antioxidant and standard treatment groups. Total thiol, glutathione, and vitamin C blood concentrations were significantly lower in RA patients at baseline compared to controls, whereas MDA-marker was significantly higher. In the same group, the concentration of markers changed significantly after antioxidant treatment ($P<.001$). The small sample size, the lack of information about antioxidant vitamin dosages, lack of power calculation, and short trial length make this trial data of limited value when making clinical recommendations for patients. From a safety perspective, cardiovascular risk factors, including low plasma carotenoid levels, have been reviewed in the literature.[30]

Antiinflammatory Agents: OA and RA Clinical Studies

*Ginger (*Zingiber officinale*)*

Ginger is believed to affect prostaglandin, thromboxane, cyclooxygenase, and lipoxygenase pathways, thus inhibiting inflammation.[31] Ginger is available as an oral product and topical cream (eg, ZingiberRx, HealthSonix, Inc, Irvine, California). Our search found no clinical studies using ginger to treat patients with RA. Regarding patients with OA, a 6-month, double-blind, placebo-controlled crossover trial was conducted with 23 patients to evaluate the effect of Zintona EC (ginger 250 mg, Dalidar Pharma, Beer Sheva, Israel) vs placebo four times daily for knee OA pain.[32] Each period of the trial lasted 12 weeks (with no washout period). At the end of week 24, study participants could elect to continue taking ginger for another 24 weeks. A validated version of the visual analog scale (VAS) WOMAC was used to evaluate pain at 4-week intervals. At the end of the first 12 weeks, both groups had a statistically significant ($P=.001$) reduction in pain scores, but the difference between groups was not significant. After the crossover period, patients switching into the ginger group had a continued reduction in VAS scores, whereas the placebo group's VAS scores increased. Two patients in the ginger group experienced heartburn. The authors used intent-to-treat analysis (assuming treatment failure for missing data). Limitations included a very small sample size, lack of washout period, lack of power calculation, substantial placebo response, and possible unblinding due to ginger's taste. This study does not support the use of ginger in the treatment of knee OA.

Another randomized, double-blind crossover study compared the efficacy of standardized ginger extract (Eurovita extract-33) 170 mg (standardized content of hydroxyl-methoxyphenyl compounds), ibuprofen 400 mg, or placebo three times daily in the treatment of 56 OA patients.[33] Primary outcomes were measured at initiation and completion of each 3-week treatment phase using the Lequesne index (a 10-question interview-like survey), 100-mm VAS for pain, as well as range of motion. The effect of ibuprofen was significantly greater than that of ginger or placebo ($P<.0001$). The small sample size, lack of appropriate washout period, and short trial duration may have impacted the validity of these results.

Haghighi et al reported no differences between 30 mg ginger extract and 1200 mg ibuprofen daily for 1 month in patients with moderate to severe OA.[34] They used multiple comparisons in a double-blind, randomized, placebo-controlled clinical trial. Pain reduction as measured by VAS was equivalent in both the ibuprofen and ginger groups compared to placebo.

The efficacy of 255 mg EV.EXT 77 (ginger and galanga) two times daily in the treatment of knee OA was evaluated in a 6-week, randomized, placebo-controlled, double-blind study.[35] Galanga is an herb believed to have antiinflammatory action via prostaglandin synthesis. The primary outcome measure was the portion of participants experiencing at least a 15-mm reduction in pain on a 100-mm VAS. Intent-to-treat (247 patients) and per-protocol analyses were performed (194 patients). The withdrawal rate was 28% in the ginger/galanga group and 16% in the placebo group (statistical significance not provided). Based on the intent-to-treat analysis, 63% of the ginger/galanga group were "responders" compared to 50% of the placebo group ($P=.048$). The per-protocol analysis showed a nonsignificant difference in VAS scores between the groups ($P=.083$). The rate of adverse effects was relatively high in this trial, reported in 59% of ginger/galanga patients and 37% of placebo patients. No statistically significant difference was reported in the incidence of serious adverse events between groups. Most adverse effects were gastrointestinal (ie, nausea, dyspepsia), and 70% of them were classified as mild by the investigators. The authors did not provide information about the frequency of use of

the rescue analgesic acetaminophen. The high placebo response rate plus the lack of power calculation make it difficult to assess the benefits of ginger/galanga therapy from this study.

Omega-3 Fatty Acids (Eicosapentaenoic acid/Docosahexaenoic acid)

Omega-3 fatty acids are long-chain polyunsaturated essential fatty acids (PUFAs) obtained from fish oil (eg, mackerel, herring, salmon, light tuna, lake trout, halibut) and available in dietary supplements. PUFAs include omega-3, omega-6, and omega-9 types.[36] The relationship among PUFAs, eicosanoids, and cytokines is complex. Western diets are low in omega-3 and high in omega-6 PUFAs. Dietary omega-9 PUFAs, including monounsaturated fatty acids (MUFAs) in olive oil, replace omega-6 PUFAs in cell membranes and lead to increased incorporation of omega-3 PUFAs.

Examples of omega-3 PUFAs include alpha-linolenic acid (ALA) (a plant-based omega-3 fatty acid found in flaxseed, walnuts, enriched eggs, and green leafy vegetables), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is the precursor of EPA and DHA. EPA and DHA, the active constituents of omega-3 fatty acids, have antiinflammatory activity by affecting metabolism of cells within the synovial joint.

EPA and DHA may inhibit the conversion of arachidonic acid to the proinflammatory eicosanoids PGE_2 in macrophages as well as inhibit LTB_4-mediated neutrophil adherence and chemotaxis. In vitro studies show EPA and DHA suppress synthesis of proinflammatory TNF-α and IL-1B that are involved in free radical formation by way of increasing iNO2 in synoviocytes.[37] EPA and DHA may also decrease synthesis of IL-6 by endothelial cells and decrease IL-1 alpha and COX-2.[37]

A fishy aftertaste is the most common adverse effect reported after consuming EPA/DHA-containing dietary supplements. EPA is a precursor of thromboxane-A3 (TXA_3) and LTB_5, which may reduce platelet aggregation and increase risk of bruising and bleeding at doses higher than 3 g daily. Theoretically, EPA/DHA-containing supplements could interact with other medications and supplements, including aspirin, NSAIDs, garlic, ginkgo biloba, vitamin C, and vitamin E.

Our search did not reveal any controlled studies in humans to support the use of omega-3 fatty acids in OA pain management. A review of omega-3 fatty acids in RA indicates that multiple studies have used combinations of EPA and DHA for treatment of RA.[38] Most studies showed improved clinical symptoms in patients including the number of tender joints, duration of morning stiffness, and/or physician pain assessment score.[38] Total EPA/DHA combined daily doses ranged from 1.04 g to 7.1 g (mean, 3 g). Treatment periods ranged from 12 to 52 weeks (mean, 16 wks). NSAIDs and slow-acting antirheumatic drugs (SAARDs) were continued throughout the trials with EPA/DHA. Overall, a trend toward benefit of reducing symptoms was demonstrated in most of the trials.

A double-blind, placebo-controlled, randomized, parallel study evaluated the effects of a liquid dietary supplement containing omega-3 fatty acids (1.4 g EPA, 0.211 g DHA), omega-6 fatty acid gamma-linolenic acid (0.5 g), ALA (16 mg), vitamins, trace elements, and other ingredients daily for 4 months in 66 patients with RA.[39] Patients had to be stabilized on corticosteroids and/or DMARDs for at least 2 months. Investigators found no change in tender joint count, the primary endpoint, from either the liquid supplement or placebo. The study was powered to detect a difference in tender joint count of 4. Study authors concluded that omega-3 fatty acids and other ingredients in combination could not be recommended for the treatment of RA.

In a randomized controlled trial (RCT), 50 subjects with RA took either a 40-mg/kg daily dose of Pikasol capsules standardized to 60% omega-3 (EPA/DHA ratio not reported; Lube AS, Hadsund, Denmark) or placebo control capsules (50/50 corn/olive oil) for 15 weeks.[40] Omega-6 fatty acid (gamma-linolenic acid) intake was <10 g daily. Results indicated a 20% improvement in six of the nine American College of Rheumatology clinical variables (ACR-20) for patients in the active arm at 15 weeks ($P<.02$) but not at 4 or 8 weeks. The variables that did not improve in patients in the active treatment arm were tender joint count, erythrocyte sedimentation rate, and C reactive protein level. A high dropout rate occurred in both arms. No side effects were reported during the study. Background nonprescription or prescription NSAID or steroid medication use during the study period was not discussed, making it difficult to establish if omega-3 fatty acids have a place in treatment of RA.

A 24-week RCT 3-arm study, sponsored by Astra Zeneca (London, UK), enrolled 60 patients with active RA stabilized on antirheumatic medications for at least 3 months as well as corticosteroids and/or NSAIDs for at least 1 month prior to the study.[41] Patients received 6 weeks of dietary counseling, 12 weeks of treatment, and a 6-week follow-up. Patients were asked to control their diet to less than 12.5 g daily of omega-6 fatty acid from cooking oils. Patients were randomized to receive either Omacor (Lovaza) 3.36 g daily (EPA+DHA=840 mg/1-g capsule; Cardinal Health, UK) or placebo. Control group participants were given no dietary counseling and did not change their diet. Twenty-five patients were withdrawn from the study due to medication-related issues from illnesses other than RA. One patient in the EPA/DHA group, and one placebo patient achieved the ACR 20% improvement criteria. At 24 weeks, serum IL-6 and TNF-α were significantly lower in the Omacor group ($P<.05$). Serum C-reactive protein concentration decreased in the Omacor group ($P<.05$). Differences were not found in tender joint count, swollen joint count, VAS pain score, patient global assessment, and modified health assessment questionnaire for all three groups. Power was not reported. Although surrogate inflammatory markers improved, more information is needed to recommend omega-3 fatty acids in higher doses for the treatment of RA.

Proudman et al conducted an open-label 12-week study in DMARD-naïve patients with RA.[42] Predefined treatment regimens included methotrexate weekly, folic acid daily, sulfasalazine daily, hydroxychloroquine daily, plus EPA/DHA total 4 to 4.5 g from cod liver oil daily. At 3 months, remission was seen in

29% of patients and increased to 54% at 3 years. By 3 years, at least one of the triple therapy combination DMARDs was discontinued in 17 patients due to gastrointestinal events. Higher doses of omega-3 fatty acids need to be further studied in RCTs in patients with RA.[43]

One meta-analysis of 17 RCTs studying the use of omega-3 fatty acids vs placebo as adjunct to NSAIDs in patients with RA or joint pain secondary to inflammatory bowel disease and dysmenorrhea for 3 to 4 months has been published.[44] Outcomes included patient-assessed joint paint, physician-assessed joint pain, duration of morning stiffness, number of painful and tender joints, RAI score, and NSAID consumption. Based on the results of this meta-analysis, a reduction in most outcomes was reported with the exception of significant effects of omega-3 fatty acids on physician-assessed pain or RAI.

Cat's Claw (Uncaria tomentosa, Uncaria guianensis)

Cat's claw is the name given to certain types of woody vines that grow in the Amazon.[45] Two of the most commonly used species are *Uncaria tomentosa* and *Uncaria guianensis*. *Uncaria tomentosa*'s active ingredients were at first believed to be oxindole alkaloids that stimulate the immune system, yet this was counterintuitive for conditions like arthritis.[46] Further analysis showed that *Uncaria guianensis* has greater antioxidant potency than *Uncaria tomentosa*, even though the oxindole alkaloid concentration in the latter is 35 times higher.[47]

The potential utility of cat's claw in treating arthritis has been related to the inflammatory response. Several in vitro experiments have shown that cat's claw inhibits the production of IL-1, TNF-α, and NF-κβ in an OA model.[48] *Uncaria guianensis* has also been shown to stimulate production of insulin-like growth factor I (IGF-I) that promotes cartilage repair.[49]

Our systematic search revealed four RCTs of cat's claw for the relief of arthritis. The first double-blind, placebo-controlled study involved 45 men with radiographic evidence of knee OA.[46] The study used *Uncaria guianensis* tablets containing 100 mg of extract in a product now registered as Vincaria (Rainforest Nutritionals, Inc, Phoenix, Arizona).[50] Patients were randomly assigned to receive 100 mg daily (n=30) or placebo (n=15) for 4 weeks. For those taking cat's claw, significant improvements were found compared to placebo for pain on activity, overall patient pain assessment, and overall physician pain assessment. Significant differences were found after 1 week ($P<.01$), with further improvements in weeks 2 and 4 ($P<.001$). However, no significant differences were found for pain at rest or at night or for knee circumference.

The *Uncaria guianensis* extract Vincaria has been evaluated as part of combination OA therapies. An RCT tested cat's claw and Sierrasil (SierraSil Health Inc, Beaverton, Oregon), a natural product containing several minerals from the Sierra Mountains.[50] In this trial, 107 patients with knee OA were randomized to one of four groups: Sierrasil 3 g daily, Sierrasil 2 g daily, Sierrasil 2 g daily plus Vincaria 100 mg daily, or placebo. All treatment groups had greater improvements in pain and physical activity compared to placebo, especially during the first 4 weeks of the trial. Statistically significant benefits were recorded at 1, 2, and 4 weeks. By the eighth week, however, the improvements remained but were no longer statistically significant compared to placebo. The researchers attributed the later results to increased use of rescue analgesia by those in the placebo group.

The only other RCT involving cat's claw in arthritis patients again used it in combination.[51] Ninety-five patients with mild-to-moderate knee OA were randomly assigned to receive either glucosamine sulfate (1500 mg daily) or Reparagen (Park Labs, LLC, Raleigh, North Carolina; 1800 mg daily). Reparagen capsules contain 300 mg Vincaria with 1500 mg *Lepidium meyenii*, a vegetable from the Andes Mountains with IGF-I activation potential. The primary outcome was a 20% reduction in WOMAC pain scores. This was achieved by almost half the participants in each group within 1 week and by approximately 90% of each group when the study concluded at week 8. Both groups also showed significant improvements at secondary outcomes measuring stiffness and overall performance. Significantly less rescue analgesia was used by those in the Reparagen group ($P<.01$). Based on the three studies reviewed in patients with OA, cat's claw can be recommended for patients with OA.

The safety and efficacy of an extract of *Uncaria tomentosa* was evaluated in one RCT for RA.[52] Forty patients were randomly assigned to either 60 mg of *Uncaria tomentosa* extract or placebo for 24 weeks. Patients in the group receiving cat's claw had significantly fewer painful joints ($P=.044$) compared to placebo, but overall pain, swelling, and stiffness were not significantly different. In a second phase of the study, patients from both groups received the herbal extract for 28 additional weeks. Outcomes improved in both groups but not to the point of statistical significance. Larger RCTs are needed to evaluate the use of cat's claw in patients with RA.

Antioxidant and Antiinflammatory Agents: In Vitro Studies

Zyflamend

Zyflamend (New Chapter, Brattleboro, Vermont) is a dietary supplement promoted as a polyherbal antiinflammatory and antioxidant agent.[53] The product contains extracts of 10 herbs (Table).

Some of the individual constituents in Zyflamend have been reported to have antiinflammatory and anticancer properties.[54] The product inhibits 5-lipooxengnase (5-LOX) and 12-LOX expression in vitro.[55] Zyflamend suppresses osteoclastogenesis and TNF-induced invasion. It potentiates cytotoxicity via downregulation of NF-κβ activation and NF-κβ-regulated gene products.[54]

No human clinical trials have investigated the use of Zyflamend nor any of its component herbal extracts in the treatment of RA or OA, with the exception of turmeric. In vitro research conducted on the individual formulation components (eg, Baikal skullcap, barberry, Chinese goldthread, ginger, green tea, Indian holy basil, hu zhang, oregano, rosemary [including one mouse study], and turmeric) is discussed here.

Baikal Skullcap (Scutellaria baicalensis)

Baikal skullcap contains a number of biologically active

TABLE Content of Zyflamend per Two Softgel Capsules[53]

Plant (Botanical name)	Alleged Active Components	Amount
Rosemary (*Rosmarinus officinalis*) leaf 100 mg supercritical extract and 50 mg extract (23% total phenolic antioxidants [TPA]-34.5 mg)	Rosmarinic acid, camphor, borneol, cineol	150 mg
Turmeric (*Curcuma longa*) rhizome 10 mg supercritical extract (45% turmerones-4.5 mg) and 100 mg ethanolic extract (7% curcuminoids-7 mg)	Curcumin	110 mg
Ginger (*Zingiber officinale*) rhizome 54 mg supercritical extract (30% pungent compounds-16.2mg, 8% zingiberene-4.3 mg) and 46 mg ethanolic extract (3% pungent compounds-1.4 mg)	Gingerol, shogaol, paradol	100 mg
Holy basil leaf (*Ocimum sanctum*) extract (2% ursolic acid-2 mg)	Ursolic acid, eugenol, rosmarinic acid, methyl chavikol	100 mg
Green tea (*Camellia sinensis*) leaf extract (45% polyphenols-45 mg)	Epigallocatechin, epigallocatechin gallate, epicatechin gallate	100 mg
Hu zhang (*Polygonum cuspidatum*) root and rhizome extract (8% resveratrol-6.4 mg)	Resveratrol	80 mg
Barberry (*Berberis vulgaris*) root extract (6% berberine-2.4 mg)	Berberine	40 mg
Chinese goldthread (*Coptis trifolia*) root extract (6% berberine-2.4 mg)	Berberine	40 mg
Oregano (*Origanum vulgare*) leaf supercritical extract (4% TPA-1.6 mg)	Carvacrol, linalool, rosmarinic acid, thymol	40 mg
Baikal skullcap (*Scutellaria baicalensis*) root ethanolic extract (17-26% baicalein complex, including baicalein and baicalin- 3.4-5.2 mg, and 0.4-0.9% wogonin-0.08-0.18 mg)	Baicalin, baicalein, wogonin	20 mg

flavonoids. Two of these, baicalein and baicalin, scavenge hydroxyl radicals and alkyl radicals in a dose-dependent manner.[56] In vitro studies summarizing the effects of Baikal skullcap on COX-1, COX-2, and 5-LOX enzymes have been published elsewhere.[57]

Barberry (Berberis vulgaris)

The antiinflammatory activity of barberry has been attributed to the constituent berberine.[58] In vitro and in vivo studies have shown that berberine decreases PGE_2, COX-2, and TNF-α.[59,60]

Chinese Goldthread (Coptis trifolia)

Constituents include the alkaloids berberine, coptisine, palmatine, epiberberine, jatrorhizine, groenlandicine, and magnoflorine.[61] An extract of Chinese goldthread and the constituent berberine inhibit IL-1β and TNF-α production via the regulation of NF-κβ signal in hepatocellular carcinoma, human G2 (HepG2) cells in vitro.[62]

Ginger (Zingiber officinale)

Constituents of ginger root inhibit COX-1, COX-2, 5-LOX, and TNF-α in vitro.[63] Animal studies suggest that 6-gingerol inhibits the synthesis of PGE_2 and TXB_2.[64] Four RCTs investigated the use of ginger extract for treatment of OA.[32-35] Results were discussed earlier in this review.

Green Tea (Camellia sinensis)

Green tea consists of polyphenols and alkaloids, including caffeine. The green tea polyphenols include epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC).[65]

In vitro research has shown that green tea polyphenols inhibit TNF-α induction in macrophages by attenuating NF-κβ activation.[66] Similarly, EGCG inhibits lipopolysaccharide (LPS)-stimulated nitric oxide production and iNOS gene expression in peritoneal macrophages by decreasing NF-κβ in vitro.[67] EGCG inhibits IL-1β-induced expression and activity of COX-2 and iNOS in human chondrocytes derived from OA cartilage in vitro.[68]

Indian Holy Basil (Ocimum sanctum)

Preliminary in vitro evidence has shown that a constituent of the leaves and stems of Indian holy basil inhibits COX and LOX pathways.[69] The essential oil of Indian holy basil has antiinflammatory activity against PGE_2, leukotrienes, and arachidonic acid-induced paw edema.[70]

Hu Zhang (Polygonum cuspidatum)

Hu zhang, also called Japanese knotweed or Mexican bamboo, is used in traditional Chinese medicine as an analgesic, among other indications.[71] Major constituents include emodin, resveratrol, physcion, and piceid.[72] Extracts of hu zhang have in vitro antioxidant and antiinflammatory activities such as inhibition of NF-κβ, one of the constituents that promotes the inflammatory response.[71]

Oregano (Origanum vulgare)

One in vitro study evaluated the antiinflammatory effect of oregano.[73] In vitro effects may be due to inhibitory effect on aldose reductase and lipoxygenase.

Rosemary (Rosmarinus officinalis)

The topical antiinflammatory activity of different extracts of rosemary leaf was tested using the croton oil ear test in mice. Main antiinflammatory constituents were identified as the triterpenes, ursolic acid, oleanolic acid, and micromeric acid.[74]

Turmeric (Curcuma longa)

Turmeric is a widely used culinary herb that gives the yellow color to curry and mustard. Made from the rhizome of *Curcuma longa*, it has many uses in Ayurveda.[75,76] Recent attention has focused on its antiinflammatory properties believed to be due to an antioxidant, curcumin (diferuloylmethane).[77] However, curcumin has limited bioavailability due to poor absorption and rapid metabolism.[78]

In vitro studies have shown that curcumin inhibits production of COX-2 enzymes, prostaglandins, and other compounds involved in inflammation.[79] It also suppresses the activation of NF-κβ. Curcumin also has been shown to counteract a number of biochemical pathways involved in RA.[80]

The only published study of turmeric in RA patients was a 1980 preliminary RCT that assigned 18 patients to either 1200 mg curcumin or 300 mg phenylbutazone.[81] After 2 weeks, patients in both groups had significant improvements in morning stiffness, walking time, and swelling compared to baseline. The improvements were generally greater in the phenylbutazone group. A number of other outcomes did not show improvements. No clinical trials using turmeric alone for OA were identified.

A crossover RCT in 42 OA patients was conducted using a multicomponent product.[82] Patients were randomized to receive Articulin-F (two capsules, three times daily) or placebo for 3 months. Each capsule contained 50 mg turmeric root, 100 mg *Boswellia serrata*, 450 mg *Withania somnifera* (ashwagandha), and 50 mg of Ayurvedic zinc complex. After 3 months, the treatment group had significant improvement in the mean pain severity score ($P<.001$) and mean disability score ($P<.05$). No power analysis was reported. Radiological assessment did not show any significant changes in either group. Since the product contained several ingredients, definite conclusions cannot be made regarding the efficacy of turmeric for OA.

Turmeric was studied in combination with *Boswellia carteri* in another RCT.[83] Sixty participants were enrolled, with 30 OA patients receiving the herbal combination (quantities not given), 15 OA patients receiving placebo, and 15 people without OA acting as controls. No details were given on how randomization was carried out. The authors stated this was a crossover trial, but the methodology was that OA patients took their capsules every 8 hours for 3 months, and there was no mention of a crossover period. After 2 and 3 months, those taking the herbal remedy had significantly better outcomes compared to placebo. Measurements made were pain-free walking time, pain on passive movement, pain after active movement, degree of tenderness, and knee effusion. Compared to the controls, patients with OA had significantly higher serum nitric oxide, superoxide dismutase, and CD4+ T cell levels. All levels decreased significantly more in those taking the herbal remedy compared to placebo. The article mentioned that two preliminary studies have shown that *Boswellia* species can relieve OA symptoms, making it difficult to determine turmeric's contribution to these results. A small number of studies in humans have shown that turmeric is tolerated well.[84]

DISCUSSION

Many dietary supplements are claimed to provide pain relief for patients suffering from OA or RA (eg, glucosamine sulfate, chondroitin, MSM). Few clinical studies or review articles evaluate antioxidant and antiinflammatory agents for the same.[85] When evaluating any clinical studies pertaining to RA, one should compare study outcomes utilizing the Rheumatoid Arthritis Disease Activity Index, Ritchie Articular Index, or the American College of Rheumatology's subjective and objective measures of disease activity to ensure content accuracy and validity. Core endpoint criteria for high-quality studies include the following: tender joint count, swollen joint count, patient assessment of pain, patient and physician global assessment of disease activity, patient assessment of physical function, and laboratory evaluation of one acute phase reactant. For OA studies, the WOMAC assessment should be conducted. Very few of the studies reviewed here evaluated clinical outcomes according to these criteria.

Next, limitations to interpreting results of RA clinical studies include the fact that disease severity for RA waxes and wanes. Baseline blood levels for markers of oxidative stress (ie, malondialdehyde) and inflammation (ie, C reactive protein level, erythrocyte sedimentation rate) also may vary pretreament and posttreatment and should be monitored.

Background baseline pretreatment antioxidant blood levels should be conducted for comparison posttherapy when studying antioxidant dietary supplements for pain management. Further, diet may influence study outcomes and must be carefully controlled for antioxidant and antiinflammatory food intake (eg, omega-3 fatty acids, omega-6 fatty acids, omega-9 fatty acids), as placebo responses are large especially in studies with omega-3 fatty acids if diet is not monitored.

Some placebo products in studies contain other constituents suspected of having antioxidant and/or antiinflammatory activity themselves, including vitamin E or olive oil, so if EPA-/DHA-containing omega-3 fatty acid dietary supplements contain vitamin E, the placebo arm should also contain vitamin E.

Future studies should take into account concurrent OTC and prescription NSAIDs and DMARDs and make their reduced use an outcome endpoint.

CONCLUSIONS

Three clinical trials support the use of cat's claw as an antioxidant/antiinflammatory agent, alone or in combination with other ingredients, for OA. Higher doses of omega-3 fatty acids are supported for the treatment of RA; however, more well-designed studies are needed to better establish the efficacy and safety of each agent. We cannot recommend use of vitamin E alone; vitamins A, C, and E in combination; ginger; turmeric; or

Zyflamend or any of its constituents (including turmeric) for the treatment of OA or RA or omega-3 fatty acids for patients with OA. Whether any of these supplements can be effectively and safely recommended to reduce NSAID or steroid usage remains unclear based on currently published literature.

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