Are Ginger and Willow Bark Extracts Viable Alternatives to Treat Osteoarthritis?

**Summary:** In a multicenter, double-blind study 261 patients with osteoarthritis (OA) of the knee and moderate to severe pain were randomized to receive either 255 mg of a ginger rhizome extract (Zinaxin, or EvExt 77, Eurovita International A/S, Karlslund, Denmark) or placebo two times per day (morning and evening with meals) for six weeks. The “ginger” extract used in the trial was a combination of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) and greater galangal (*Alpinia galanga* L., Zingiberaceae). The authors report that 255 mg of the encapsulated product is extracted from 2,500–4,000 mg of dried ginger rhizome and 500–1,500 mg of dried greater galangal rhizome. The placebo capsules contained coconut oil. Acetaminophen (maximum daily dose of 4 g) was permitted as a rescue medication (i.e., drugs that are allowed to be used to manage symptoms during a study). The primary efficacy variable was the proportion of responders experiencing at least a 15 mm reduction in knee pain on standing between baseline and the final visit as measured by a 100 mm visual analog scale (VAS). Secondary efficacy measures were: 1) average improvement in pain on standing as measured by the VAS; 2) consumption of rescue medication; 3) Western Ontario and McMaster Universities (WOMAC) OA composite index as measured by VAS, with one end of the scale being “no pain/stiffness/difficulty” and the other end being “extreme pain/stiffness/difficulty” (the total score was calculated as the mean response); 4) patient assessment of OA status (global status) over a 24-hour period using a 5-point Likert scale (1 = very poor and 5 = very good); 5) quality of life assessment; and 6) pain in the knee after walking 50 feet. Efficacy and safety assessments were performed at baseline and after 2 and 6 weeks of treatment.

Using an intent-to-treat analysis, 247 patients (ages 52 to 78 years) were included in the evaluation at the end of the trial. The overall withdrawal rate was 28 percent in the ginger group and 16 percent in the placebo group — withdrawal due to adverse events (gastrointestinal complaints were most common in the ginger group) was 13 percent (n = 17) and 5 percent (n = 6), respectively. A greater percentage of patients taking ginger experienced a reduction in knee pain on standing of ≥15 mm compared to the placebo group (63 percent vs. 50 percent; p = 0.048). The analysis of means for pain on standing showed that the ginger group improved an average of 8.1 mm more than the placebo group (p = 0.005). Considering those with a pain improvement of ≥20 mm, the ginger group again showed a statistically greater number of responders than the placebo group (n = 73 [59 percent] vs. n = 56 [46 percent]; p = 0.036). When this was extended to pain reduction of ≥25 mm, the ginger group continued to show a response superior to placebo (n = 65 [52 percent] vs. n = 48 [39 percent]; p = 0.035). On secondary measures, patients taking ginger had a significantly greater reduction in mean values of knee pain on standing (24.5 mm vs. 16.4 mm; p = 0.005) and reduction in knee pain after walking 50 feet (15.1 mm vs. 8.7 mm; p = 0.016). Reduction in the WOMAC composite index was not statistically significant (12.9 mm vs. 9.0 mm; p = 0.087). Change in global status and reduction in intake of acetaminophen was numerically greater (but not statistically significant) in the ginger group but there were no differences between groups on the change in quality of life measure. Gastrointestinal adverse events were more common in the ginger group, (116 events in 59 patients [45 percent]) compared to the placebo group (28 events in 21 patients [16 percent]). None of these gastrointestinal adverse events were considered serious by the investigators (belching, dyspepsia, and nausea were most commonly reported).

**Summary:** In a double-blind trial, 86 patients with OA of the hip or knee were randomized to receive either two tablets of a willow bark extract (extracted from *Salix purpurea* L. and *Salix daphnoides* Vill., both of family Salicaceae) or placebo two times per day (morning and noon, one half hour before meals) for two weeks. The extract (provided by Salus Haus GmbH, Bruckmühl, Germany) was standardized to 17.6 percent salicin and was placed in tablets containing 340 mg of extract (provided by Zeller AG, Romanshorn, Switzerland) providing approximately 60 mg of salicin (a total daily dose of 240 mg of salicin). Patients were not allowed to take any medications for pain or inflammation during the study and each patient went through a 4 to 6 day washout period before beginning the study. Patients were assessed at intake (prior to the washout period), baseline, and days 7 and 14. The primary out-
come measure was the pain score on the WOMAC index. Secondary outcome measures included the physical function and stiffness dimensions of the WOMAC index, daily visual analogue scales (VAS) on pain and physical function (completed by the patient), as well as physician assessments.

Seventy-four patients completed the trial. During the trial, four patients (three placebo, one willow bark) withdrew due to pain and need for pain medication, and one patient in the willow group withdrew due to allergic symptoms (skin rash). Patients taking willow had a statistically significant improvement in the WOMAC index pain score compared to placebo (mean difference of 6.5 mm; p=0.047). This translated to a 14 percent reduction in pain score for the willow bark group versus an increase of 2 percent in the placebo group. However, physical function and stiffness measures on the WOMAC showed no statistical difference between groups. Patient assessment and physician assessment of change of disease activity was significantly better in the willow group compared to placebo (p=0.0002 and p=0.00073, respectively). Adverse events were reported more frequently in the placebo group (28 events in 16 patients) compared to the willow bark group (17 events in 16 patients). Skin complaints (including the previously mentioned rash) were most common in the willow bark group while gastrointestinal complaints were most common in the placebo group.

Comments/Opinions: Clinical management of OA is primarily aimed at symptom relief. While exercise and physical therapy may help slow the condition, most patients with OA are forced to use analgesics and/or anti-inflammatory drugs to manage their symptoms. A degenerative chronic disease, OA often leads to the eventual need for hip or knee replacement surgery.

The introduction of the COX (cyclooxygenase)-2-specific inhibitor class of drugs (e.g., fexofenadine hydrochloride and celecoxib) has offered an anti-inflammatory alternative with less gastrointestinal side effects than the nonsteroidal anti-inflammatory drugs (NSAIDs); however, little is known about the long-term safety of these drugs. Like NSAIDs, these COX-2 inhibitors are associated with adverse renal effects in some patients.

This rather bleak picture has led many OA patients to seek alternative therapies to manage their condition and hopefully slow progression of the disease. The 1997 Harvard survey of alternative medicine use in the U.S. found that 27 percent of people with arthritis had used an alternative therapy for their disease within the last year. A 1999 Gallup questionnaire found that among arthritis sufferers, 28 percent thought that herbal supplements might have a role in managing their condition. Although not an herbal supplement, one need look no further than the hugely popular dietary supplements glucosamine sulfate (glucosamine hydrochloride is a less seldom used form) and chondroitin sulfate to realize the popularity of alternative approaches to treating OA.

The two clinical trials summarized above offer healthcare professionals a glimpse at two herbs that may provide an alternative to COX-2 inhibitors or NSAIDs for management of pain and inflammation. However, the question that needs to be asked in both cases is how effective these alternatives to drug therapy are when considering efficacy and safety with regular use.

The ginger trial is certainly the superior trial of the two. While the study was completed before widespread acceptance of the full WOMAC index (which is now the standard in OA clinical trials), the trial uses a more homogenous patient base (knee OA only) and is longer in duration (six weeks) than the willow bark trial (two weeks). Although the reduction in knee pain was significant for patients taking ginger versus placebo, an editorial in the same issue of *Arthritis & Rheumatism* suggests that the WOMAC scores reported in this trial did not find statistical significance compared to placebo. The authors of the editorial also point to the fact that the 8.1 mm difference for knee pain on standing is “quite modest.”

![Ginger Zingiber officinale. Photo © 2002 stevenfoster.com](Image)

With regard to compliance, one must wonder at the large number of patients in the ginger group complaining of gastrointestinal side effects. While ginger is traditionally used to treat gastrointestinal upset, the use of very concentrated extracts may prove problematic due to heartburn and other related symptoms.

Although earlier case reports have been published on the use of ginger for rheumatic disorders including OA, the current trial is only the second randomized trial to be published on the use of ginger for OA. The earlier trial used another Euryvita ginger extract (EV.ext 33) with a standardized hydroxy-methoxy phenyl compounds and delivered in soft-gel capsules. The product contains only “Chinese ginger” (the Latin binomial is not given) and not the greater galangal and ginger combination used in the current trial. The trial compared the efficacy of 510 mg/day of the ginger extract with ibuprofen (1200 mg/day) and placebo for treatment periods of three weeks each in a double-blind, crossover trial with 75 patients with OA of the hip or knee. While the trial found a significant difference in pain relief between ibuprofen and placebo, the difference between ginger and placebo was not significant. Interestingly, there was a statistically significant effect between ginger and placebo prior to the first crossover but not in subsequent treatment periods. The design of this trial and the short duration of each treatment period may have been insufficient to properly test the efficacy of the ginger extract.

The more recent trial uses a completely different product that combines ginger with greater galangal. In their introduction, the
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Authors correctly point out that ginger and greater galangal are both in the family Zingiberaceae. However, their use of the term "ginger" to describe both species is something I have been unable to verify in the botanical literature. While there are references to Alpinia officinarum being commonly called either Chinese galanga or Chinese ginger, there are no references to A. galanga being referred to as ginger (please note that A. chinensis (Retz.) Roscoe, Zingiberaceae is also referred to as Chinese galanga). This makes the comparison of the two controlled trials on ginger for OA virtually impossible. Apparently, the selection of the two species used in this trial was based on an earlier assay of anti-inflammatory activity in animal models.

While the use of ginger as an analgesic is a relatively new use for the herb, willow bark has a long history of use for rheumatic conditions. The German Commission E approves its use for diseases accompanied by fever, rheumatic ailments, and headaches. Use of the herb is based on daily dose of the constituent salicin. While the Commission E recommends 60 to 120 mg of salicin per day, this range has been increased to 240 mg/day in the more current ESCOP monograph for willow bark.

The current study looking at the use of willow bark extract for OA follows on the heels of a small pilot study that reported the use of 1,360 mg/day of a willow bark extract delivering 240 mg of salicin was somewhat effective in treating pain associated with OA of the knee or hip. A larger randomized trial with 210 people complaining of low back pain found that 240 mg/day of salicin was more effective than 120 mg/day for pain relief (both were statistically superior to placebo). These results were supported in a recent phase IV study.

Salicin is converted to salicylic acid in the liver and intestines. Interestingly, the authors of the study report their own unpublished findings of a pharmacokinetic study that found that oral administration of 240 mg/day of salicin in 10 healthy volunteers led to a peak level of salicylic acid in the serum of 1.4 mg/L. In contrast, 500 mg of acetylsalicylic acid (aspirin) leads to peak serum levels of salicylic acid ranging from 35 to 50 mg/L. Earlier reports have suggested that 240 mg/day of salicin is roughly equivalent to 50 mg of aspirin — a cardioprotective but not analgesic dose. While popular focus has been on willow bark and specifically, salicin as aspirin alternatives, there are clearly other constituents that are contributing to the action of willow bark in the treatment of pain and inflammation. Finally, as aspirin is rarely used as an analgesic for OA, these comparisons must extend to the more commonly used NSAIDs and COX-2 inhibitors.

On the other side of the coin, one is forced to compare both ginger and willow bark to the more popular supplements glucosamine sulfate (GS) and chondroitin sulfate (CS). As opposed to NSAIDs and COX-2 inhibitors, as well as ginger and willow bark, GS and CS not only led to pain reduction but are also thought to be chondroprotective (protective of cartilage cells). A meta-analysis of randomized trials on GS and CS for OA was published in the March 15, 2000 issue of the Journal of the American Medical Association. While the authors criticize many of the trials for methodological problems that may have led to overzealous reporting of results, an accompanying editorial suggests that these are also found in trials with NSAIDs. The authors of the meta-analysis conclude that, overall, "it seems probable that these compounds do have some efficacy in treating osteoarthritis symptoms and that they are safe. Because of this, they may have considerable utility in osteoarthritis treatment.

Following this meta-analysis of the effects of glucosamine sulfate and chondroitin sulfate, the Lancet published the findings of a 3-year randomized, placebo-controlled trial using 1,500 mg/day of GS in 212 patients with OA of the knee. Interestingly, the change in the WOMAC index was statistically significant between groups (34.1 percent difference; p=0.016). Notable were statistically significant improvements in the both the WOMAC pain (p=0.020) and physical function (p=0.047) subscales. Perhaps most interesting clinically was the finding that joint-space narrowing in the medial compartment of the tibiofemoral joint did not decrease in the GS group while there was a significant mean and minimum loss of joint-space. These results suggest that long-term use of GS not only effectively reduces symptoms of OA but may also slow the degeneration of the affected joint.

Practice Implications: While longer clinical trials are needed to explore the efficacy and safety of either ginger or willow bark extracts in the symptomatic treatment of OA, the results of these recent clinical trials suggest that both may have a modest effect in managing pain. Clinicians interested in recommending either of these herbal alternatives need to consider the risk to benefit ratio versus conventional drug therapies such as NSAIDs and COX-2 inhibitors. Finally, the results of clinical trials (particularly the most recent 3-year trial) with GS suggest it may be the most efficacious alternative therapy for the long-term treatment of OA. ❧
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examines the effect on LH and FSH on this population for a longer period of time (e.g., six months). It is also important that women in this population be informed that the study used only 40 mg of the Remifemin® extract daily. While the earlier pharmacological study found no evidence of a hormonal effect at 127 mg/day, the study was completed with women reporting no history of breast cancer.

Practice Implications: Although larger and longer clinical trials are needed, these new data suggest that black cohosh may not effectively treat menopausal symptoms, such as hot flashes in women who are breast cancer survivors — particularly those taking tamoxifen (although reports of sweating were significantly reduced in women using black cohosh). While not a definitive comment on the safety of black cohosh in this population, the study does suggest that black cohosh does not affect LH and FSH, therefore supporting an earlier study that found no estrogen-like activity in women without a history of breast cancer.

Reference: