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Management of Osteoarthritis with Avocado/Soybean Unsaponifiables

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Abstract

Osteoarthritis (OA) is a painful and life-altering disease that severely limits the daily activity of millions of Americans, and is one of the most common causes of disability in the world. With obesity on the rise and the world's population living longer, the prevalence of OA is expected to increase dramatically in the coming decades, generating burdensome socioeconomic costs. This review summarizes current pharmaceutical, non-pharmaceutical, and prospective new treatments for OA, with primary focus on the dietary supplement Avocado/Soybean Unsaponifiables (ASU). ASU modulates OA pathogenesis by inhibiting a number of molecules and pathways implicated in OA. Anticatabolic properties prevent cartilage degradation by inhibiting the release and activity of matrix metalloproteinases (MMP-2,3,13) and increasing tissue inhibitors of these catabolic enzymes (TIMP-1). ASU also inhibits fibrinolysis by stimulating the expression of plasminogen activator inhibitor (PAI-1). Anabolic properties promote cartilage repair by stimulating collagen and aggrecan synthesis via inhibition of inflammatory cytokines such as IL1, IL6, IL8, TNF, ERK, and PGE2. Chondroprotective effects are mediated by correcting growth factor abnormalities, increasing TGFβ while decreasing vascular endothelial growth factor (VEGF) in synovial fluid. ASU also inhibits cholesterol absorption and endogenous cholesterol biosynthesis, which mediate reactive oxygen species pathology in chondrocytes. At the clinical level, ASU reduces pain and stiffness while improving joint function, resulting in decreased dependence on analgesics.

Author Contributions

All authors were fully involved in preparation of the manuscript.

Keywords

Osteoarthritis; cartilage; dietary supplements; avocado soybean unsaponifiables (ASU); Arthrocen

Introduction

Osteoarthritis (OA) is a chronic synovial joint disease, characterized by two main features: 1) progressive damage of articular cartilage, bone remodeling and new bone formation (osteophytes and subchondral bone sclerosis), and 2) synovial inflammation and fibrosis of ligaments, tendons, menisci, and capsules. All joints may be affected, but the most commonly involved are knees, hands, and hips (Fig. 1). While chronic OA used to be regarded as a "wear and tear disease," researchers now believe that low grade inflammation and growth of blood vessels and nerves from the subchondral bone into articular cartilage, as well as metabolic disorders, play a major role in disease pathology.[1–4] Patients with OA suffer from pain, inflammation, and limited joint function. Pharmacological interventions are mostly palliative, focusing on alleviation of symptoms or slowing disease progression until damaged hip or knee joints are eventually replaced.[5–10] Women are more severely impacted than men by knee osteoarthritis.[11] Differences in knee anatomy (narrower femurs, thinner patellae, larger quadriceps angles, and differences in tibial condylar size), previous knee trauma, genetic and hormonal influences may play a role. Other factors like age, and obesity, are also common factors. In general, women present for treatment in more advanced stages of osteoarthritis and have more debilitating pain than men. Women also have less cartilage volume and greater cartilage wear, and overall differences in mechanical alignment.

Current Pharmacologic Therapies

Pain medications currently used to treat the symptoms of OA include acetaminophen, topical capsaicin, topical and oral nonsteroidal anti-inflammatory drugs (NSAIDs i.e. naproxen and ibuprofen), and the synthetic opioids tramadol and codeine. However, each of these therapies has potential drawbacks that may limit their widespread use. Analgesics can be addictive, while acetaminophen can have serious side effects, such as kidney and liver damage.[12] Patients who do not respond to acetaminophen may be prescribed NSAIDs. Treatment with NSAIDs, which inhibit cyclooxigenaeses (COX1 and COX2) thereby blocking prostaglandin synthesis, improves quality of life and decreases pro-inflammatory cytokines including interleukin 6 (IL6), vascular endothelial growth factor (VEGF), and tumor necrosis factor alpha (TNFα) in synovial fluid and mitogen-activated protein kinases (MAPKs) in knee OA.[13] However, NSAIDs can also cause serious side effects, including upper gastrointestinal (GI) toxicity (dyspepsia, ulcers, perforation, obstructions and bleeding) and liver dysfunction. As such, they are typically prescribed for the shortest possible duration at the lowest effective dose. To reduce the risk of these upper GI complications, the US FDA has approved the use of the NSAID HZT501 (Duexis®), a drug containing 800 mg ibuprofen, in combination with 26.6 mg famotidine, a histamine H2-receptor antagonist.[14] Alternatively the NSAID celecoxib has less risk of upper GI complications by selectively inhibiting the isoenzyme COX-2, which is specific to inflamed

tissue, versus COX-1, which is constitutive in many tissues including the GI tract. It should be noted that daily treatment with celecoxib is more effective in patients with normal BMI than obese patients.[15]

Intra-articular injection of corticosteroids (GC) is recommended to relieve inflammation and pain in OA joints. However, GC injections are short acting, prone to adverse side effects, and have limited disease-modifying effects. For patients with knee OA, viscosupplementation with hyularonin may be used to replaces shock absorbing and lubricant material in the joint fluid, but the effects are similarly short-lived.

Current Non-Pharmacologic Therapies

Currently, guidelines for OA management are available from numerous organizations, including the American Academy of Orthopedic Surgeons (AAOS), the American College of Rheumatology (ACR), the American Geriatrics Society (AGS), the American Pain Society (APS), and the Osteoarthritis Research Society International (OARSI) in the US, and the European League Against Rheumatism (EULAR) and the United Kingdom's National Institute for Health and Clinical Excellence (NICE) in Europe. Collectively, these guidelines reflect the experience of physicians across a variety of medical disciplines. While all generally use the same data sources (i.e., evidence-based research, expert opinion, patient experience, and cost-effectiveness analysis), they differ in focus. For instance, the AAOS and AGS guidelines reflect the perspective of specialists in orthopaedic surgery, geriatrics, and pain management, while the EULAR and OARSI guidelines primarily emphasize the findings of experts in rheumatology. The NICE guidelines are developed jointly by physicians and other healthcare professionals working in conjunction with a range of clinical researchers. In addition, the scope varies, with some guidelines (e.g., AAOS, ACR, EULAR, and OARSI) addressing specific types of OA (i.e., knee, hip, or hand) and others (e.g., AGS, APS, and NICE) addressing OA more generally. As such, recommendations can vary widely; for instance, guidelines for use of NSAIDS.[10, 16–19] Recommended non-pharmacologic interventions range between therapeutic exercises, patient education, transcutaneous electrical nerve stimulation, acupuncture, orthotics and insoles, heat and cryotherapy, patellar tapping, and weight control. In an effort to evaluate these varying guidelines, The Appraisal of Guidelines Research and Evaluation (AGREE II) scored 17 clinical practice guidelines (CPGs) including EULAR, NICE, OARSI, AAOS, and ACR, on six different measures-- D1: scope and purpose, D2: stakeholder involvement, D3: rigor of development, D4: clarity and presentation, D5: applicability, and D6: editorial independence.[20] The general clinical management recommendations tended to be similar among high-quality CPGs, although interventions addressed varied. Non-pharmacological management interventions were superficially addressed in more than half of the selected CPGs.

Prospective New Treatments

New non-invasive, disease-modifying therapies for OA are lacking and needed by millions of patients. A number of prospective new treatments targeting proinflammatory mediators,

cytokines, bone turnover, angiogenic and neurogenic factors are being investigated, with varying success in clinical trials and clinical use.[21]

Interleukin 1 (IL1) may prove a effective target, as IL1 induces matrix metalloproteinase (MMP) production, resulting in the degradation of aggrecan and other matrix constituents. IL1 also induces high levels of COX2 and prostaglandin E2 (PGE2), which may explain the pain associated with OA degeneration.[22] The drug diacerein, an inhibitor of IL1, may modify both disease symptoms and disease-structure in OA. Oral diacerein has proven effective in reducing pain, although evidence from clinical trials and scientific literature suggest that the effectiveness in OA is weak. It can be used in conjunction with NSAIDs or viscosupplementation therapies for additive effects due to its alternative mechanism of action. The most common side effects of diacerein are gastrointestinal, such as diarrhea and changes in the color of urine. Meanwhile, the IL1-receptor antagonists, anakinra and orthokin are reported to improve Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores,[23–25]. In addition, the IL1β antibody “gevokizumab” is in phase II clinical trials for safety and biological activity in the treatment of hand OA.[26, 27]

Nerve growth factor (NGF) has also been recognized as an important mediator of chronic pain in OA. Tanezumab, a monoclonal antibody against β-NGF receptor tyrosine kinase (TrkA) inhibits NGF action and reduces pain in patients.[28] Two randomized phase III clinical trials indicate that tanezumab provides superior pain relief while improving physical function and global disease assessment scores in patients with painful hip OA.[27, 29–33] While in most cases tanezumab is well tolerated, the unexpected occurrence of rapid destructive arthropathies suggests there may be safety issues. Alternatively, using the drug adalimumab to inhibit TNFα, which upregulates β-NGF, does not improve global disease assessment scores in OA of the hand.[27, 34]

Several studies have explored therapies aimed at modifying bone turnover for treatment of osteoarthritis. Strontium ranelate (SrRa), an element similar to calcium, is easily taken up by the body and incorporated into bones in place of calcium. SrRa is currently indicated for the prevention of fracture in severe osteoporosis. The SEKOIA (**S**rRa **E**fficacy in **K**nee **O**steoarthr**I**tis tri**A**l) trial, a 3-year randomized, double-blind, placebo-controlled trial, evaluated the efficacy, safety and disease-modifying effects of SrRa given at 1–2 g/day in patients with knee OA. MRI data indicate that SrRa significantly reduced cartilage volume loss and bone marrow lesion progression. Symptoms also improved in terms of pain and physical function after 6 and 12 months respectively,[35] while treatment was deemed safe and well tolerated. These data indicate that SrRa could be a promising new symptom and disease-modifying treatment for OA. Additionally, there is a need for further investigations to establish the optimal dosage and to better clarify the mechanism of action of SrRa in OA.[35–37] Several clinical studies have investigated the effects of anti-resorptive therapies such as bisphosphonates on OA symptoms. A study by Carbone *et al.* found that alendronate use in OA patients decreased bone abnormalities and attenuated knee pain, yet cartilage degeneration was still present in the MRI scans of treated patients.[38] Spector *et al.* determined that risedronate use led to significant improvements in WOMAC scores and preservation of knee joint space compared to placebo in a one-year randomized control trial involving patients with moderate OA.[39] However, a 2-year randomized control trial of

risedronate treatment revealed contradictory results, with no significant improvement of WOMAC score or joint space retention in the knee.[40] Similarly, Nishii *et al.* observed no inhibition of osteoarthritis progression in treated hip OA patients after 2 years of ALN treatment.[41] Therefore, in spite of the growing body of clinical work investigating the subject, no definitive conclusion can be reached on the practicality of using bisphosphonates to treat patients with OA.

Anti-depressants have shown promising preliminary results for treatment of pain associated with OA by increasing serotonin levels in the brain. Serotonin-norepinephrine reuptake inhibitors duloxetine (Cymbalta) and milnacipran significantly improve pain in OA,[27, 42]. An open-label trial also suggested analgesic effectiveness of methotrexate, and anti-inflammatory drug that acts by inhibiting the metabolism of folic acid, demonstrating that up to 20 mg/week for 6 months achieved OARSI responder criteria in knee OA and warranted a randomized controlled trial.[43]

Other treatments are aimed at improving disease pathology by building cartilage. The small molecule kartogenin was identified in an image-based high-throughput screen to promote chondrocyte differentiation. It shows chondroprotective effects *in vitro* and is efficacious in two animal models of OA. Kartogenin induces chondrogenesis by disrupting the interaction between filamin A and the transcription factor core-binding factor b subunit (CBFβ), thereby altering CBFβ-RUNX1 and possibly RUNX2 transcriptional programs.[44] Autologous injection of platelet-rich plasma (PRP) has been used to stimulate cartilage repair and healing in OA patients,[27, 45, 46] but the presence of other growth factors in PRP may be problematic. Furthermore, Bone morphogenic protein 7 (BMP7), FGF-8, and botulium toxin A (BoNT-A), are used in the treatment of knee OA.[47] BoNT-A has an analgesic effect by temporarily suppressing acetylcholine secretion at pre-synaptic nueuromuscular junctions, and appears to be effective and safe for the management of advanced knee OA. However, these results cannot be generalized to patients with mild knee joint pain or nonspecific soft tissue pain in the knee joint region. Further research is necessary to investigate possible complications such as aggravation of infection, effect on muscle strength, and neuropathic joint degeneration.

Current nonsurgical and reconstructive surgical therapies are unsuccessful in reversing OA. Recently a phase I trial was reported in which chondrocytes were modified via intra-articular DNA injection to produce TGF1 in patients with advanced knee OA,[48]. Intra-articular injection of adipose-derived stem cell (ADSC) therapy in the new European program is also under investigation.[49] ADSC induced the release of trophic factors that exerted anti-inflammatory effects on both synoviocytes and chondrocytes, with no MMP1, MMP3 or MMP13 production, suggesting safe and effective use of ADSCs for clinical applications. However, both treatments need proof-of-concept studies in larger patient populations. Alternatively, intra-articular injection of human mesenchymal stem cells can lead to articular cartilage protection through the SDF-1/CXCR4 axis.[50–54]

Dietary Supplements

Natural products can be safer than prescription medications with less undesirable side effects. Dietary supplements including avocado soybean unsaponifiables (ASU), chondroitin sulfate, hyaluronan and glucosamine sulfate have been reported to modify EULAR symptoms for the treatment of OA.[55, 56] They are used to treat mild to moderate pain, and alleviate symptoms to reduce the consumption of NSAIDs.

Several trials for chondroitin sulfate, glucosamine sulfate, and hyaluronan $(C_{14}H_{21}NO_{11})^n$ are in process.[56, 57] Chondroitin sulfate, glucosamine sulfate and hyaluronan are building blocks for proteoglycan synthesis, and major constituents of the ECM in cartilage and synovial fluid.[58] They are produced by chondrocytes and syonivocytes or obtained through diet.[59–65] Hyaluronan and hyaluronic acid (Hyalgan® hylan-GF20 / Synvisc®) can be injected into the knee joint of patients with oateoarthritis who cannot tolerate NSAIDs, or are awaiting joint surgery.[66] A recent report indicates that viscosupplementation with Hylan-GF20 slows type II collagen degradation and joint inflammation in patients with OA.[67] However Hylan-GF20 was not present in granulomas, an indicator of inflammation, raising the question of clinical significance in pain reduction,[68]. Also, viscosupplementation with hyaluronic acid itself does not significantly improve disease outcome, and little is known about long-term effects.

The efficacy of glucosamine and/or chondroitin in treating knee OA pain was evaluated in the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), funded by the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS). Patients were treated daily for 24 weeks with glucosamine alone (1500 mg), chondroitin sulfate alone (1200 mg), glucosamine and chondroitin sulfate combined (same doses), a placebo, or celecoxib (200 mg), which served as a positive control. While there were no statistically significant differences between any of the experimental treatments and the placebo overall, patients with moderate-to-severe pain given both glucosomine and chondroitin sulfate did show improvement (79% experienced pain reduction versus 54% for placebo). Because of the small size of this subgroup these findings should be considered preliminary and need to be confirmed in further studies.[61, 69–71]

Glucosamine does not appear to slow arthritis progression over the long term, and has many potential complications. The most common adverse effects are epigastric pain or tenderness, heartburn, diarrhea, and nausea. Glucosamine also may cause allergic reactions in patients with seafood allergies, as a product of lobster, crab, and shrimp shells. Glucosamine may interact with various pharmaceuticals, such as warfarin (Coumadin) and diabetes medications, dangerously modifying their efficacy.

Similarly, chondroitin sulfate appears not to provide meaningful benefit for patients with OA, and their combination has not proven effective for either pain management or functional improvement. OARSI and NICE no longer recommend the use of glucosamine or chondroitin sulfate alone, or in combination, if no effects are observed after six months or radiographic changes are marginal.[55, 61, 62, 72]

A network meta-analysis of 10 trials in 3803 patients by Juni and collaborators in 2012 found no clinically significant improvements in OA pain alleviation or JSN parameters with glucosamine, chondroitin, or combined treatment compared to placebo. Despite these results, many patients believe otherwise, potentially due to the natural course of disease, regression to the mean or the placebo effect. The authors conclude that such patients should be permitted to use these supplements if they cover the cost themselves, since neither of these preparations was found to be dangerous.[73]

SierraSil is a dietary supplement marketed for joint pain relief that is derived from the mineral-rich clay found in the high Sierra Mountains in the US. Clinical trial testing short-term efficacy of SierraSil at doses of 2 and 3g per day failed to show sustained benefits over placebo, and iron toxicity has been reported.[74]

Some OA patients experience pain relief from topical creams containing capsaicin, the active component of chili peppers. However, use of these creams may introduce side effects such as burning, stinging, and redness of the skin and eyes.[10]

Avocado and Soybean Unsaponifiables

Avocado/soybean unsaponifiables (ASUs) are natural vegetable extracts made from avocado and soybean oils, consisting of the leftover fraction (approximately 1%) that cannot be made into soap after saponification chemical reaction. ASU is composed of one third avocado and two thirds soybean unsaponifiables (A1S2U). The major components of ASU are phytosterols β-sitosterol, campesterol, and stigmasterol, which are rapidly incorporated into cells. ASU is a complex mixture of many compounds including fat-soluble vitamins, sterols, triterpene alcohols and possibly furan fatty acids. The identity of the active component(s) remains unknown. The sterols content of ASU preparations are the primary contributors to biological activity in articular chondrocytes[75]. Preclinical *in vitro* and *in vivo* studies have demonstrated that ASUs have beneficial effects on OA.[76–90]

ASU possesses chondroprotective, anabolic and anticatabolic properties. It inhibits the breakdown of cartilage and promotes cartilage repair by inhibiting a number of molecules and pathways implicated in OA (Fig. 2). ASU stimulates the synthesis of collagen and aggrecan by inhibiting inflammatory cytokines such as IL1, IL6, IL8, TNF, and PGE2 through modulation of NF-kappaB.[91–94] The combination of ASU and epigallocatechin gallate (EGCG, a major component of green tea catechins), affect an array of inflammatory molecules including expression of COX-2 and production of PGE2 in chondrocytes.[95] COX-2 regulates the production of PGE2; both are mediators involved in the process of cartilage breakdown. ASU also inhibits the release and activity of collagenase (MMP2) and stromelysin 1 (MMP3) in cultured chondrocytes,[77, 96] increases tissue inhibitors of metalloproteinases (TIMP-1),[79, 97] and inhibits IL-1 induced ERK but not p38 or JNK in chondrocytes *in vitro*.[86]

In vitro studies show that ASU inhibits fibrinolysis by stimulating the expression of plasminogen activator inhibitor (PAI-1).[98] PAI-1 inhibits tissue plasminogen activator and urokinase (uPA), thereby blocking plasminogen activation and inhibiting fibrinolysis (the physiological breakdown of blood clots). This fibrinolytic and tissue destructive proteinase

cascade may play a role in OA joint inflammation via altered expression of uPA receptors.[99]

ASUs alters growth factor levels implicated in OA pathogenesis, increasing TGF-β1 and TGF-β2 in the canine knee joint fluid,[100] to repair cartilage and decreasing VEGF, which is markedly elevated in synovial fluid of patients.[13, 97] In a study of implant osseointegration in rat tibiae, ASU administration improved markers of bone growth, including bone morphogenic protein 2 (BMP-2) and transforming growth factor beta 1(TGF-β1), though histomorphometric analysis of implant osseointegration was only slightly improved.[101] ASU also inhibits cholesterol absorption and endogenous cholesterol biosynthesis.[102] 60% of patients with OA exhibit high levels of oxidized low-density lipoproteins (oLDL) in serum, which mediates reactive oxygen species (ROS) activity in chondrocytes and OA pathology.[103, 104] Treating patients with a daily dose of 300 mg ASU for 3 months decreased oLDL levels.[105]

At the clinical level, ASU reduces pain and stiffness while improving function in joints, resulting in decreased dependence on analgesics. ASU efficacy and safety during and post treatment have been assessed in various randomized, double blind, multicenter trials in patients with symptomatic knee or hip OA. Two studies conducted over a 3 month period report that standard treatment with 300 mg/day of ASU improved indices of pain, stiffness, and physical function, as measured by WOMAC, and decreased analgesic drug demanded in patients with OA.[106–109] A third trial conducted over 6 months reports similarly improved function compared to placebo, measured by the Lequense Functional Index, with persistent effects after termination of treatment.[108] In a 6-month trial on patients with femorotibial gonarthrosis, ASU was as effective as 400 mg of chondroitin sulfate three times per day, as measured by WOMAC.[110] Most recently a three-year randomized trial on patients with hip OA, performed under the ACR criteria (minimum of 1–4 mm hip JSW on the pelvic radiographs), reports excellent safety, but no significant reduction in the mean rate of JSN after one year. However, analyzing the results under different parameters reveals a significant 20% reduction in the rate of progression in patients with severe hip OA ($p = 0.04$), indicating a potential structure modifying effect of ASU,[111] as confirmed in the ERADIAS study. In a clinical trial of patients with hip OA, the effects of ASU treatment over 3 years were evaluated by radiography to identify joint pathology and disease progression on the structural level. Although JSN was not statistically significant between ASU and placebo treatment, secondary analysis of disease progression, measured by JSN (0.5 mm) or total hip replacements, indicated 20% improvement with ASU (42.2% versus 51.4% of placebo group, $p=0.054$). Computerized image analysis also showed significant histological differences not detectable by traditional scoring methods.[112] In sheep, ASU treatment following cartilage insult improved articular integrity, as measured by toluidine blue staining, after 6 months compared to untreated animals. These improvements were the result of decreased catabolism and increased anabolism of cartilage by ASU.[78] Indeed, ASU reduces inflammation mediated cartilage degradation by reducing IL-1, PGE2 and MMP-3 production, while also inducing proteoglycan, non-collagenous protein (NCP) and collagen synthesis within 72 hours of administration to bovine cells in culture.[75] A recent study in patients with nonspecific dorsalgia demonstrated analgesic effect of Piascledine with positive outcome after one month.[113] However, a randomized, double blind, placebo-

controlled clinical trial carried out in 14 obese adult volunteers over 3 months reports no significant effect on these parameters, as measured by hyperglycemic-hyperinsulinemic clamp technique.[114]

Four double-blind placebo-controlled randomized human clinical trials (RCTs) evaluate ASU's impact on knee and hip OA.[109] Two of these indicated that ASU treatment decreased NSAID intake over 3 months.[106, 107] Another found that ASU improves Lequense Functional Index (LFI) compared to placebo over the course of 6 months, and also that improvements took 2 months to take effect, and subside after treatment ended.[108] Alternatively, a long-term study indicated no significant difference in JSN, or other parameters of disease, after 2 years of ASU treatment,[80] indicating that the beneficial impact of ASU on OA may be limited to short-term effects. However, this study also focused on identifying structure-modifying effects, versus symptom-modifying effects; while these two different measures of OA severity often correlate, ASU may impact each uniquely. Evidence for symptom modifying effects of ASU is much stronger, and thus an alternative explanation for these contradictory findings is that while ASU does not improve structural damage of OA, as measured in this study, it does improve symptoms such as pain and mobility, as measured in previous studies.[82] In a study of chronic nonspecific back pain, treatment with ASU (piascledine) combined with the NSAID artrosiline (320 mg/day) showed significant analgesic effect over NSAID treatment alone. The positive effect of ASU was demonstrated after one month of treatment. The authors suggest that further RCTs are needed to confirm results. To this end, the ERADIAS trial determined whether ASU Expanscience™ treatment slowed the radiological progression of hip OA.[113] As for safety, none of the four RCTs reported significant differences in adverse effects between ASU and placebo.

Factors like BMI, severity of disease and activity level may influence the effect of ASU, as these conditions exacerbate inflammatory conditions and mechanical stresses that contribute to OA. Adipose tissue plays an important role by producing metabolic factors with catabolic and proinflammatory properties, including cytokines, chemokines and adipokines (IL-6, and TNF-α, IL-8, IFN gamma), which orchestrate pathophysiological processes in OA. Soluble mediators produced by adipocytes may also modulate chondrocyte metabolism and contribute to cartilage degradation. ASU may counteract these inflammatory processes by inhibiting the translocation of the transcription factor NF-κB from the cytoplasm to the nucleus, which controls transcription of many proinflammatory factors.[86, 115] As such, ASU acts as an anabolic agent in vitro, reducing the production of pro-inflammaotry mediators, including IL-1, IL-6, IL-8, macrophage inflammatory protein-1, NO, MMP-13, TNF-α, and COX2/PGE2[88, 94, 115, 116] from various cell types. In mice, ASU decreases proinflammatory interferon-gamma (IFNγ) and IL4 production, in the context of parasitic diseases.[117, 118] While more studies need to be conducted to show the effects of ASU in patients with varying BMI, the anti-inflammatory effects of ASU are likely to protect cartilage from obesity-associated inflammatory degradation and improve OA symptoms. Indeed, ASU significantly decreased the rate of OA progression to 40% compared with 50% in the placebo group in one study.[111] However, this study showed that ASU did not influence the rate of OA progression in the obese subset of patients with mean symptom duration 4 and BMI of 27 kg/m^2.

However, excessive inflammation associated with obesity may also impede efficacy, as it does with celecoxib (NSAID) treatment, which is not as effective in obese patients (BMI in excess of 30 kg/m^2).[119] The influence of obesity, and how it influences ASU efficacy may also depend on the parameters used to measure and define disease. In a study examining the relationship between BMI and OA in patients scheduled to undergo hip replacement, increasing BMI was associated with increasing levels of pain and functional disability, but not radiographic joint damage. Thus, obesity might influence some aspects of disease and treatment, but not others. This should be taken into account when designing and assessing studies intended to examine the impact of obesity on treatment efficacy.[119]

ASU has anti-inflammatory effects in mice when administered in conjunction with the anti-parasitic drug Praziquantel, reducing inflammatory cytokines interferon-gamma (IFNγ) and IL4, as well as granuloma size, while increasing cidal activity.[117, 118] ASU also protects gingival elastic fibers from degradation by human leukocyte elastase,[120] hypodermatitis,[121] and ischemic damage.[122]

A recent electronic databases analysis demonstrated the benefits and harms of oral medicinal plant products in treating osteoarthritis. The authors used standard methods for trial selection and data extraction, and assessed the quality of the body of evidence using the GRADE approach for major outcomes such as pain, function, radiographic joint changes, quality of life, withdrawals due to adverse events, total adverse events, and serious adverse events. The ASU product Piasclidine® formed a small and clinically questionable improvement in symptoms, compared to placebo after three to 12 months treatment. Radiographic joint changes, as change in joint space width (JSW) did not differ between ASU 300 mg treatment and placebo. Moderate-quality evidence from a single study confirmed possible benefits of ASU 600 mg over placebo. There is no evidence that Piasclidine significantly improves joint structure, and limited evidence that it prevents joint space narrowing. Authors suggest further investigations are required to determine optimum daily doses producing clinical benefits without adverse events.[123]

ASU is considered as drug in most countries, and therefore is prescribed by physicians. However, in United States it is classified as dietary supplement, and can be purchased as over-the-counter supplements, Avoca ASU (ASU-NMX1000, Nutramax Laboratories Inc., Edgewood, MD, USA), and Maximize ASU 300 / SierraSil (Maximum International Inc. Pompano Beach, FL). Avoca ASU, a combination of ASU and glucosamine sulfate, has been shown to suppress TNFα, IL1β, COX2, iNOS, PGE2, NFκB activation and nitrite production in articular chondrocytes and monocytes/macrophages, reducing pain and inflammation in OA patients.[115, 116, 124] However, conflicting reports indicate the complete absence of specific ASU molecules in Avoca ASU when compared with Piascledine.[75, 125–127]

Questions remain about the efficacy and safety of ASUs for treatment of OA (Table 4). Macaigne and colleagues published a case report in 2004 describing a female with lymphatic colitis associated with Piascledine treatment.[128] Further prospective multicenter studies are warranted to investigate whether other microscopic colitis cases[129] are observed in patients treated with Piascledine. Avoca ASU that contains glucosamine can induce allergic reaction

in people with shellfish allergy. Even in very small quantities, these people may experience mild symptoms, such as hives or nasal congestion, or more-severe, even life-threatening symptoms.

An alternative ASU formulation is Arthrocen (Pharmin, USA, LLC. San Jose, CA). Arthrocen is an extract from avocado and soybean oils that does not contain any ingredients of animal origin, artificial flavor, sweetener, or color; each capsule contains 100 mg unsaponifiable persea gratissima unsaponifiable (avocado) and 200 mg unsaponifiable glycine max (soybean) extracts, Silica, magnesium stearate (E470b-manufactured from vegetable oil), and gelatin fines.

In general, FDA does not held dietary supplements to the stringent standards of pharmaceutical manufacture. If ASU is to be widely used for the treatment of OA, serious consideration should be given to their current regulatory status in order to ensure potency, purity, and as well as the excipients. Many studies have demonstrated substantial variation between the content listed on the labels of these products and the actual content. The sterols content of ASU have been demonstrated to have biological activities in culture and in animal models. This approach allowed us to compare the contents of 3 commercial supplements. We found multiple peaks were present in the Piascledine-300 (Expanscience) mass spectrometry analysis (Agilent 7890 GC System, 7693 Auto Sampler, Agilent VL MSD with triple Axis Detector, Brea, California), compared to the Arthrocen 300 mg (PharminUSA) or ASU300-Avocado Soy Unsaponifiable with Sierra 600 mg (Maximize, Maximum Int.) preparations (Figure 2). Similar results were found for Piascledine-300[75] with mass spectra sterol content of C20H30O2, C20H28O2, sitosterol, stigmasterol, campesterol, squalene, beta-tocopherol, desmethyl tocopherol, oleic acid docosane, alpha-amyrin, and cholesterol. In 2 letters to the editor, Msika[126] and Henroitin[125] claimed that the exact ingredients and preparation of ASU-Expanscience was an intellectual proprietary, protected by patent. Msika further emphasized that the tocopherols, sterols and patented specific molecules from avocado contribute to the originality of the product, different from natural avocado unsaponifiables. In contrast, they analyzed Dasuquin with MSM, Dasuquin, and Avoca ASU (Nutramax), and compared them with ASU Expanscience. The analyses revealed content of products were significantly different from those indicated on the Nutramax labels—with no citrostadienol, and brassicasterol present in ASU Expanscience. Contrary to that they found contents included high level of rapeseed oil and unsaponifiables products with very low tocopherol, and without respected ratio of 1:2 for avocado to soybean unsaponifiables. The original ASU Piascledine®300 pills contains 100 mg of avocado unsaponifiables and 200 mg of soybean unsaponifiables. The difference in sterol content is based on the A/S ratio and avocado-specific modified unsaponifiables obtained by a patented process. Henrotin et al., have shown ASU effects are best when the ASU ratio are 2:1[92]. In support, Henroitin recommended additional studies to ensure efficacy of Nutramax products[125]. These issues and reported adverse effects of ASU (Table 5[128, 130]) raises concerns about the content and purity of ASU supplements on the market, with implications for patient safety.

Conclusion

Osteoarthritis inflicts pain and physical limitation on millions of people. Improving joint function and patient activity is a central public health concern to improve quality and length of life. The aim is not only to treat pain, but also to prevent the onset of disease. There is no cure for OA and even symptomatic treatment options are scarce, dominated by pain management and surgical intervention. ASUs may prove to be an effective treatment option for symptomatic OA, as they have been shown to possess chondroprotective, anabolic, and anticatabolic properties, as well as anti-inflammatory properties. At the clinical level, ASUs reduce pain and stiffness while improving joint function. Importantly, ASUs are a natural, slow-acting agent that do not merely address acute pain, but actively prevent progression of OA symptoms. Further studies are required to determine the specific mechanisms and target molecules of ASU function on OA at the cellular and metabolic level.

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Competing Interest Statement

Simi Bhatti and Ramin Goudarzi are employees of Formulation Technology Inc. and Pharmin USA, LLC, respectively. However, neither Formulation Technology nor Pharmin USA contributed funds or resources to this study or the co-authors.

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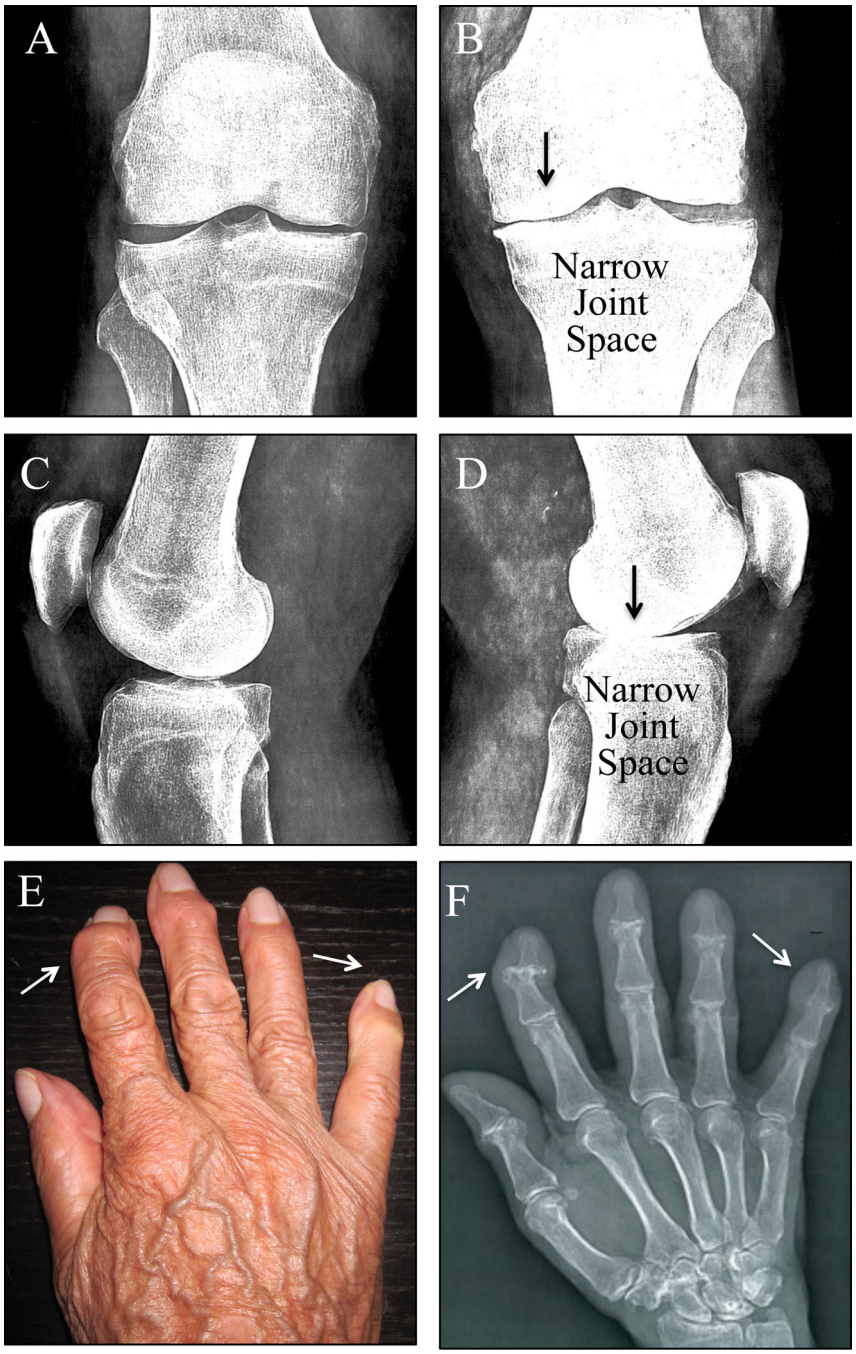

Figure 1.

Anteroposterior (A–B) and cross-table lateral (C–D) of knee osteoarthritis.

Symptomatic knee OA typically presents with narrowing of the joint space and bone spurs (arrows). During the development of OA, articular cartilage breaks down over time and become thin. As a result the bone surfaces rub against each other, further damaging the cartilage and bone, and causing pain. Joints with late stage OA are often painful, warm to the touch, possibly red, swollen, and have notable loss of function. When cartilage wears away, bones may no longer be protected from rubbing and grinding against each other,

causing pain and subchondral cysts. **Osteoarthritis of the hand (E–F).** Osteoarthritis of the interphalangeal joints of the hand. Presence of bony swelling and deformity due to osteophytes at the distal interphalangeal joints (Join Swelling and Heberden's nodes).

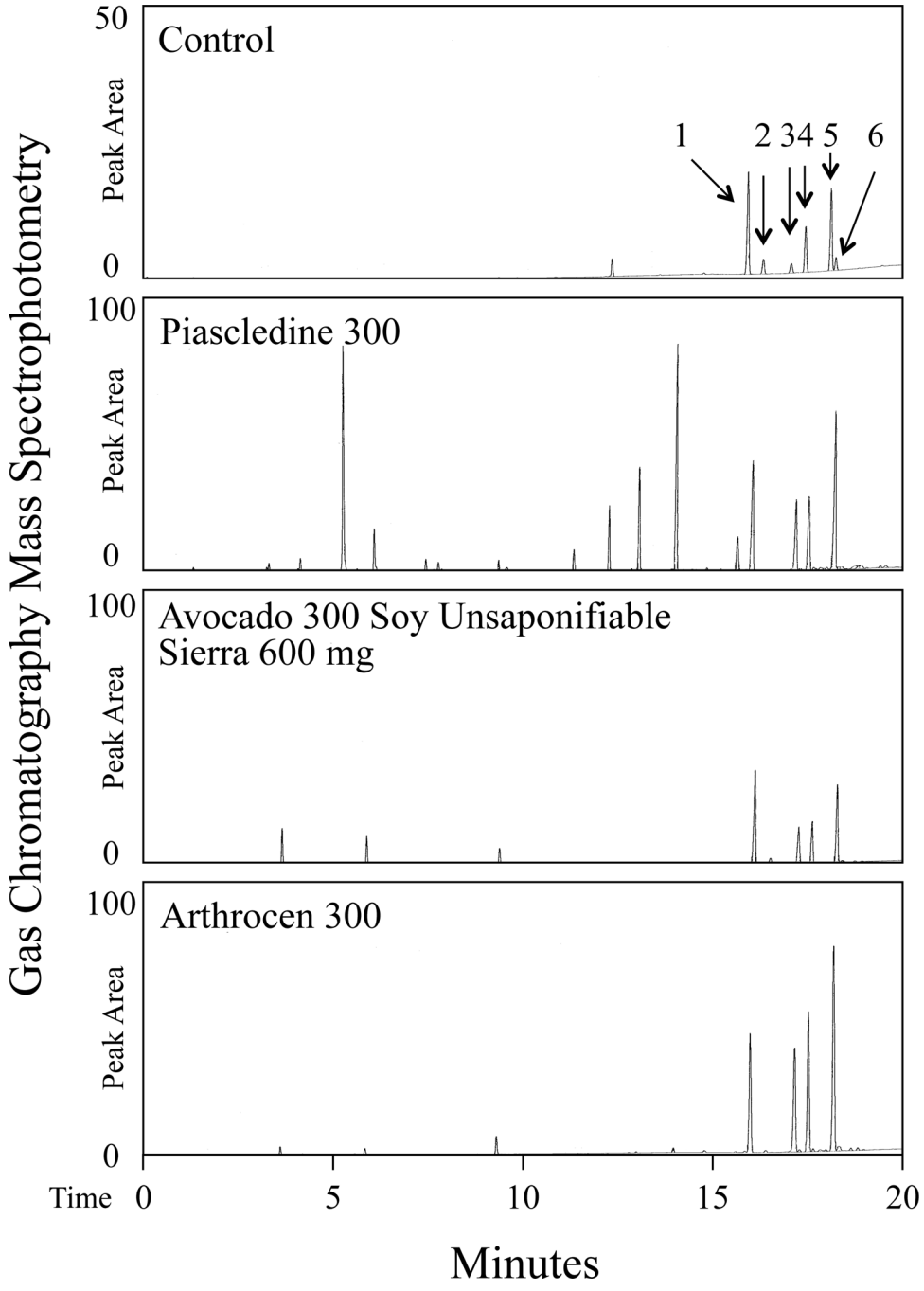

Figure 2.

Gas Chromatography-Mass Spectrometry analysis of major sterol components of Piascledine 300, Avocado 300 Soy Unsaponifiable with Sierra 600 mg, and Arthrocen 300. Control sample exhibited characteristic peaks corresponding to 1- Dihydrocholesterol (5α-Cholestan-3β-ol; internal control Sigma Aldrich), 2- Brass (Brassicasterol), 3- Camp (Campesterol), 4- Stigmn (Stigmastanol), 5- β-Sito (β-sitosterol), 6- Stigma (Stigmasterol).

Table 1

Inhibitory effects of Avocado Soybean Unsaponifiable on inflammatory and catabolic mediators of osteoarthritis

Molecular Mediator	Target Tissue/Organ	Organism	Assay	References
Interleukin-1 beta (IL1β)	Synoviocytes Chondrocytes	Mice Rabbit Human	In Vitro	77, 81, 116
Interleukin-(IL4)	Chondrocyte		In Vitro	
Interleukin-6 (IL-6)	Chondrocyte	Human	In Vitro	81, 92
Interleukin-8 (IL-8)	Chondrocyte	Human	In Vitro	92
Macrophage inhibitory protein-1beta (MIP-1β)	Chondrocyte	Human	In Vitro	87, 116
MMP-2 (also known as Collagenase, or Gelatinase-2)	Fibroblasts, Chondrocyte	Human	In Vitro	79, 81, 92
MMP-3 (also known as Stromelysin)	Fibroblasts Chondrocyte + Subchondral bone osteoblasts (SBO)	Mice Human	In Vitro	79, 81, 84, 86, 92, 101
MMP-13 Collagenase-3	Chondrocytes Chondrocytes + SBO	Mice Human	In Vivo	84, 86
Tissue inhibitors of MMP (TIMP-1)	Fibroblasts + SBO	Human	In Vitro	79, 84
COX2	Chondrocytes Monocyte/Macrophage-like cells Chondrocytes + SBO	Equine Human	In Vitro	84, 116, 115
Prostagladine-2 (PGE2)	Hyalin Chondrocytes Monocyte/Macrophage-like cells	Mice Equine Human	In Vitro	86, 92, 116
NF-κB	Hyalin Chondrocytes Nuclear translocation of p65	Mice Equine Human	In Vitro	86, 115
ERK1/2	Hyalin Chondrocytes	Mice Human	In Vitro	86
TNF-α	Chondrocytes	Human	In Vitro	84
iNOS	Chondrocytes Monocyte/Macrophage-like cells	Human	In Vitro	84, 116
NO	Chondrocytes Monocyte/Macrophage-like cells	Human	In Vitro	116
oLDL	Osteoblasts	Human	Serum	104
Fibronectin	Chondrocytes	Human	In Vitro	81
Alkaline phosphatase	Osteoblasts	Human	In Vitro	

Table 2

Stimulatory effects of Avocado Soybean Unsaponifiable on anti-inflammatory, anabolic mediators that protect against osteoarthritis

Molecular Mediator	Target Tissue/Organ	Organism	Assay	References
Collagen synthesis	Articular synoviocytes Chondrocytes, Skin fibroblasts	Rabbit Bovine Human	In Vitro	81, 84, 93
Collagen II mRNA	Chondrocytes + Subchondral Bone Osteoblasts (SBO)	Human	In Vitro	84
Agrecan Proteoglycan	Chondrocytes SBO	Equine Human	In Vitro	84, 94
TGF-β1	Knee joint fluid Osseointegration in tibiae	Rat Canine	In Vivo In Vitro	84, 98, 100, 101
TGF-β2	Knee joint fluid	Canine	In Vitro In Vivo	98, 100
TGF-β3	Chondrocytes + SBO	Human	In Vitro	84
BMP-2	Osseointegration in tibiae	Rat	In Vivo	101
Osteocalcin	Chondrocytes + SBO	Human	In Vitro	84
Chondroprotector	Bone Implant	Rat	In Vivo	96
Delayed destruction of the joints	Radiological evaluation	Human	In Vivo	81
Plasminogen activator inhibitor 1 (PAI-1)	Chondrocytes Osteoblasts	Bovine	In Vitro	98

Table 3

Content analysis of supplements containing Avocado Soybean Unsaponifiable

Company/ Manufacturer	Brand Name	Dosage Form	Other Ingredients	Excipients on the label
Nuramax Laboratories, Inc.	Avoca ASU	Avocado/Soyben Unsaponifiables, non-shellfish glucosamine, NMX1000®	OptiMSM® Methylsulfonylmeth Green tea extract	
Helseudsalg Faaborg Denmark	AvoSol	Avocado 100 mg / Soy 200 mg Unsaponifiables	Vitamin C 30 mg	Glucose syrup, ox gelatin, soy protein isolate, extract rich in tocopherol, silicon dioxide, magnesium salts from fatty acids.
Dr. Theos Official USA	Avosoy	Avocado-Soybean Unsaponifiables	Vitamin C 60 mg Vitamin E 30 U Manganese 2mg	Cellulose, dicalcium phosphate, sodium crosscarmelose, silicon dioxide, gum acacia, vegetable stearic acid, film coating, magnesium stearate
Dr. Theos Official USA	Avosoy Complete	Avocado-Soybean Unsaponifiables 300mg Glucosamine 1500mg Porcine chondroitin 800mg	Vitamin C 60 mg Vitamin E 30 U Manganese 2mg	
Swanson Health Products. Fargo, ND, USA	AvoVida	100 mg Unsaponifiables Persea gratissima Glycine max	30% β-sitosterol, campesterol, stigmasterol	Soy protein isolate, mixed tocopherols, silica Microcrystalline cellulose (plant fiber), gelatin, magnesium stearate.
Pharmin, USA, Llc. Formulation Technology, USA	Arthrocen 300 mg	Avocado 100 mg / Soy 200 mg Unsaponifiables	Persea gratissima Glycine max	Silica, magnesium stearate (E470b manufactured from vegetable oil), and gelatin fines.
Nuramax Laboratories, Inc.	Cosamin ASU	Avocado/Soyben Unsaponifiables	Glucosamine Sulafate Chondoitine Sulfate	
Maximum International USA	Maximize	ASU300-Avocado Soy Unsaponifiables SierraSil : 600 mg	Iron: 1.1 mg (from SierraSil) Iron toxicity recommendation on the container.	Microcrystalline cellulose, maltodextrin, croscarmellose sodium, silicon dioxide, stearic acid, hydroxypropylm ethylcellulose, hydroxypropylcellulos, magnesium stearate, polyethylene glycol.
Expanscience Lab., Courbevoie, France Pharmascience, Montreal Canada. Pharma Inv. Chile SA, Santiago Solvay Ins.Biol. Chenioterapicosells Microsules Y Bernabo Siegfried, Rhein	Piascledine 300	Avocado/Soybean Unsaponifiable	Not described	Butylated hydroxytoluene (BHT) 0.05 mg/Capsule Colloidal anhydrous silica

Table 4

Adverse effects of Avocado Soybean Unsaponifiable

Organ	Side Effects	Frequencies	Drug withdrawal	References
Skin	Eczema Hives Photosensitivity Hypersensiticity syndrom	32.5%		130
Liver	Liver injury Bilirubin ALKP GGTP	16.2%	Return to Normal	130
Gastrointestinal	Regurgitation Heartburn Nausea Epigastric pain Dyspepsia Diarrhea Constipation Microscopic colitis	12%	Return to Normal	106, 129, 130
Coagulation	Platelets	6.8%		130

ALKP : alkaline phosphatases GGTP: Gamma-glutamyl transpeptidase