Chapter

Evidence for the Effectiveness of Soy in Aging and Improving Quality of Life

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Abstract

Soy is a highly nutritious yet widely underutilized food. Because of the controversy surrounding soy, individuals with chronic disease states that may benefit from soy or soy isoflavone consumption may avoid this food. The relationship of soy to estrogen, breast cancer, osteoarthritis, and other chronic disease states is discussed. Osteoarthritis is a specific focus, as the immobility brought about by this disease state may lead to other chronic diseases that are also positively affected by soy consumption, and because there is no clear etiology or cure for this debilitating disease. Conclusions and future directions for soy research as it relates to healthy aging are also discussed.

Keywords: soy, osteoarthritis, aging, breast cancer, longevity

1. Introduction

Globally, life expectancy has increased by nearly 20 years in both sexes since the 1950s [1]. In the United States (US) in 2015, life expectancy at birth was calculated to be almost 79 years old for both males and females [2]. While these numbers are encouraging, the quality of life of these individuals has not increased along with this increased life expectancy [3]. There are many factors that can influence quality of life but chronic diseases such as osteoporosis, osteoarthritis, heart disease, sarcopenia, type 2 diabetes (T2D), and dementia all play a role in the quality of life (QOL) of aging individuals.

Many chronic diseases are highly preventable and are generally treatable through diet and exercise. Indeed, poor diet and inadequate physical activity are two of the three most common risk factors for several chronic diseases, and addressing these factors in addition to the third risk factor, smoking, reduces the risk of cardiovascular disease (CVD), stroke, and T2D by 80% [4]. A 2013 study which analyzed the effect of physical inactivity on chronic disease estimated that, worldwide, physical inactivity is linked to 6–10% of chronic diseases that included CVD, T2D, breast cancer, and colon cancer, and that inactivity is associated 9% of premature deaths [5].

Knee osteoarthritis (OA) has been ranked as one of the top contributors to global disabilities in the world [6]. Osteoarthritis is a degenerative disorder of synovial joints characterized by focal loss of articular cartilage with reactive changes in subchondral and marginal bone, synovium and para-articular structures [7]. These degenerative changes lead to the primary complaints of pain with movement, stiffness, instability, and loss of function, particularly in those with knee OA [8].

The World Health Organization (WHO) estimates that about 10% of individuals 60 years or older have OA, an estimate that will only increase as the world's population continues to age due to longer life expectancies [9]. The conclusive etiology of this disease is unknown, but injury to the joint, age, gender, and obesity are all known factors to contribute to the development of OA [10]. There is also mounting evidence that leptin may play a key role in the pathophysiology of OA. Leptin concentration in the serum is positively correlated with Body Mass Index (BMI) [11, 12]. This finding is significant as it helps to explain why obesity is a risk factor for OA, even in non-weight bearing joints such as hands.

Because individuals with OA are in constant pain, they are likely to stop exercising or to engage in any physical activity, thus increasing their risk of morbidity. It may also lead to other chronic diseases, both as a result of the lack of exercise, and the possibility of weight gain and the risks associated with excess weight. In fact, T2D has been shown to be a risk factor for knee OA progression [13], indicating that these disease states feed off of each other. While exercise is incredibly important for health, nutrition may be a much more helpful and significant treatment for individuals with chronic diseases, specifically OA, because the source of many of these diseases is underlying inflammation [14] and treating the inflammation through dietary change may result in the treatment of multiple disease states.

Although OA affects a large number of Americans, there are no proven therapies for preventing or halting its progression. In the normal joint, there is a balance between synthesis and degradation of cartilage. In inflammatory conditions such as OA, and other chronic diseases, catabolic molecules are upregulated, thereby interrupting the function of anabolic molecules [15]. Catabolic cytokines also induce the production of specific matrix degrading metalloproteases, causing cartilage degradation [16]. This finding has been confirmed by the increased level of these cytokines in people with OA [17]. Unregulated or excess production of these molecules may play a detrimental role in the pathophysiology of OA [16, 18].

The development of OA is also accompanied by increased production of prostaglandins (PGs), molecules that may contribute to joint damage, pain, and inflammation [19]. Cyclooxygenase (COX) is responsible for the production of PGs and exists as two distinct isoforms, COX-1, and COX-2. Increased expression of COX-2 has been demonstrated in synovial tissues suggesting that COX-2 expression mediates the inflammatory response in OA [20]. COX-2 is undetectable in most tissues, but is increased in inflammation leading to overproduction of PGE2 [21, 22]. Inhibition of these enzymes by nonsteroidal anti-inflammatory drugs (NSAID) and selective COX-2 inhibitors reduces the levels of PGs, resulting in a reduction in pain and inflammation.

Finding nutritional interventions to target the COX-2 pathway while allowing other necessary inflammatory pathways to function would significantly increase quality of life as well as functionality of individuals with OA. It may also inadvertently target unregulated inflammation that has been associated with other chronic disease states, and allow for affected individuals to exercise thus further decreasing their risk for the aforementioned chronic diseases.

Soy appears to be a promising treatment for those with OA, and has many other health benefits. Soy protein is low in saturated fat, contains all of the essential amino acids, and is also a good source of fiber, iron, calcium, zinc, and B vitamins [23]. This book chapter will focus on soy and its relationship to OA and other chronic diseases.

2. Nutrition profile of soy

Soy is a very nutritious plant, and the only complete plant protein. Protein in soy is not only high, but comparable in quality to animal protein regarding amino

acid content and digestibility [24]. The carbohydrate content of soybeans is not only low, but poorly digested by intestinal enzymes, and thus behaves as a prebiotic for beneficial bacteria [25]. The fat content is highly variable among different soybean varieties, but includes 10–15% saturated fat, 19–41% monounsaturated fat, and 46–62% polyunsaturated fat [26].

Most notably, soybeans contain isoflavones. The three main isoflavones present in soybeans include genistein (50% of isoflavones), daidzein (40% isoflavones) and glycitein (10% of isoflavones) [27]. Isoflavones are also classified as phytoestrogens because of their similar structure to estrogen (**Figures 1** and **2**). Isoflavones are more bioactive in their unconjugated (aglycon) form than their conjugated form, which must be hydrolyzed in the intestine to release the aglycons [28]. Additionally, fermented soy has more unconjugated isoflavones, thus making fermented soy foods more pharmacokinetically beneficial [29]. Soy isoflavones are also metabolized by gut bacteria, which leads to many different metabolites, the most biologically active being euqol [30]. Equol is structurally similar to estrogen, but inhibits growth of mammary tumors and may act as a selective estrogen receptor modulator (SERM) [31]. Isoflavones have anti-oxidative and anti-inflammatory properties, as well as the ability to alter gene expression, specifically in estrogen-responsive genes [32]. It is this ability that often leads health practitioners to believe that soy may be dangerous for certain populations, specifically breast cancer, which will be later discussed in this chapter. However, these SERM like capabilities are responsible for many of soy's positive effects on health.

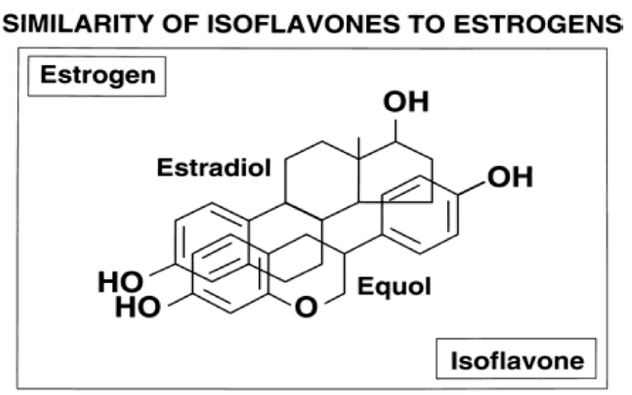

Figure 1.
Similarity of isoflavones to estrogens.

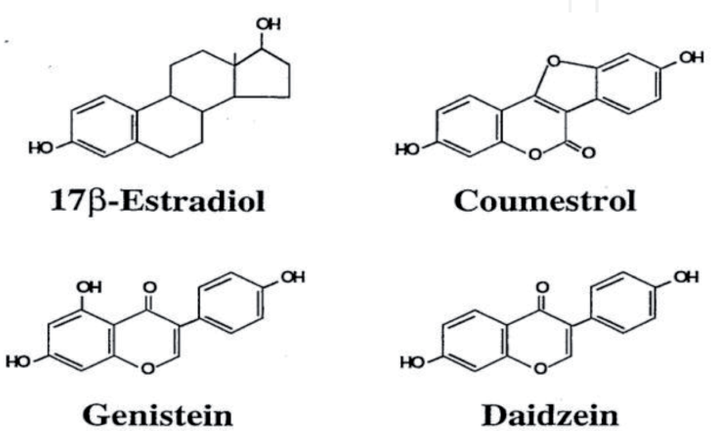

Figure 2.
Structure of estrogen and isoflavones.

3. Soy, estrogen, and breast cancer

Breast cancer is one of the most common cancers diagnosed in women in the United States, and is the second leading cause of death after lung cancer in women [33]. Breast cancer is strongly linked to ovarian hormones and estrogen levels [34]. Factors like high endogenous estrogen levels and hormone therapy have been implicated in increasing breast cancer risk [35]. Indeed, 2/3 of breast cancer cases are estrogen receptor (ER) positive [36].

Because soy isoflavones closely resemble estrogen, many health practitioners warn against soy consumption in women, women with breast cancer, and post-menopausal women for fear that soy will behave like an estrogen molecule. In our opinion, this idea is misconceived, as soy isoflavones would likely compete with endogenous estrogen for binding receptor sites in the breast, thereby reducing estrogen-stimulated growth and proliferation in the breast tissue, and may reduce endogenous estrogen concentrations [37]. Indeed, it has been shown that soy isoflavones may act as an estrogen antagonist in estrogen rich environments, and an estrogen agonist in low estrogen environments [38]; there is also evidence that the bioavailability of soy isoflavones may be inversely related to estrogen levels [39].

Epidemiological studies have shown that soy isoflavones do exert a protective effect on breast cancer risk, indicating a 16% risk reduction per 10 mg of daily isoflavone consumed [40]. A Dutch study [41] found that high levels of plasma genistein were associated with up to a 32% decreased risk of breast cancer. A 2009 study [42] that investigated soy food intake and breast cancer survival found that soy food consumption was associated with a marked decreased risk of both mortality and recurrence of breast cancer.

A 1997 study [43] found that genistein is a potent estrogen agonist and exhibited cell growth-inhibitory actions in breast cancer cells *in vitro*. A more recent study [44] also found that genistein works to inhibit topoisomerase II activity, thus resulting in the inhibition of breast cancer growth. Davis et al. [45] investigated the radioprotective effects of genistein by injecting female mice with the isoflavone 24 h prior to receiving a toxic dose of radiation, and found that genistein treated mice expressed fewer DNA damage responsive and cell cycle checkpoint genes than untreated mice. Magee et al. [46] investigated the effect of coumestrol, glycitein, daidzein, and the metabolites equol and O-desmethylangolensin on MDA-MB-231 cells, finding that each inhibited invasion by approximately 30% at the lowest dose, while genistein and coumestrol exerted the most potent inhibitory effects on invasion at the highest dose.

A clinical trial by Shike et al. [47] supplementing soy isoflavones in women with breast cancer found that soy consumption did alter gene expression in breast cancer tumors, specifically in FANCC and UGT2A1 which have both been implicated in the development of breast cancer tumors. There was a subset of tumors with upregulated FGFR2 expression, which is a marker of poor prognosis in breast cancer patients, and overall soy intake did not significantly change cell proliferation and apoptosis indices compared with the placebo group. While this initially sounds discouraging, the article points out that the clinical ramifications of this minor upregulation have yet to be determined.

Another common concern about soy supplementation in post-menopausal women, specifically, is that it causes lymphocytopenia, which is the condition of having low levels of lymphocytes in the blood. Some of these concerns stem from a multicenter study [48] published in 2001 where postmenopausal women supplemented 600 mg of ipriflavone, a synthetic isoflavone, for 3 years. Out of 234 women, 13.2% developed subclinical lymphocytopenia ($<0.5 \times 10^3/mm^3$). Another 2 year study [49] found that 3% of their participants also developed abnormal

lymphocyte numbers. Another study by Ben-Hurt et al. [50] found that postmenopausal women also had higher monocyte levels, indicating that menopause definitively alters hematological parameters.

A rat study [51] by our lab refutes these results. Our study not only found that ovariectomy increased lymphocyte, monocyte, eosinophil, and basophil differential counts, but that soy isoflavones retuned leukocyte counts to pre-surgery levels. To test the truth of this in human populations, our lab also investigated the extent to which 1 year of 25 g soy protein containing 60 mg isoflavones supplementation alters lymphocyte counts in postmenopausal women [52]. This study indicated no effect on total and differential white blood cell counts in postmenopausal women, which may be due to the fact that the estimated isoflavone content of the soy protein was lower than the pharmacological dose at 60 mg.

Because leukocyte counts tend to go up with menopause, it is not necessarily a bad side effect for pharmaceutical doses of soy to bring down white blood cell counts. Additionally, the supplementation of soy protein did not have a significant impact on leukocyte levels, indicating that soy supplementation is generally safe for healthy postmenopausal populations.

4. Soy, estrogen, and OA

Interestingly, OA is often seen in postmenopausal women, and is three times more likely to be a problem for postmenopausal women rather than men [53]. Cartilage is an estrogen sensitive tissue, which may, in part, explain the gender disparity. Because postmenopausal women experience a severe drop in the production of estrogen, it stands to reason that estrogen may be protective against the development of OA. Some studies [54–56] have found an association between hysterectomy and OA, while others [57, 58] have found no association. A study by Gao et al. [59] found that estradiol (E_2) deficiency as well as changes in estrogen metabolites are involved in the pathogenesis of OA. Increased cartilage and bone turnover has been found in multiple animal models of menopause [60], but contrary to a general belief that lack of estrogen in women is the cause of OA, Tsai and colleagues [61] have suggested that excessive level of synovial fluid estrogen is responsible for the development of OA in both men and women. Indeed, some studies have found that the direct administration of estrogen to the knee joint has increased OA instance and progression [62, 63]. Intraarticular estradiol injection to ovariectomized rabbits both upregulated ER and ultimately caused further cartilage degeneration [64].

Soy isoflavones are often referred to as phytoestrogens, and may be helpful in relieving some symptoms of OA, and possibly prevent its progression. The conformational binding of soy isoflavones is similar to that of a SERM, which have been shown to be effective estrogen agonists or antagonists [65]. Genistein is the most potent of the isoflavones, and can therefore hypothetically produce positive effects on cartilage by blocking the action of estrogen. In addition to the possibility of modulating ERs, soy isoflavones may be able to increase IGF-1 production and decrease inflammation while also acting as an antioxidant. IGF-1 is thought to slow cartilage degradation [66]. Because soy isoflavones may serve as a natural modulator of IGF-1 production, it is probable that consumption of soy would benefit people suffering from OA.

5. Soy, leptin, and OA

Leptin is of particular interest in the pathology of OA, as the severity of OA is associated with both weight and BMI [67, 68], and leptin is generally elevated in

obese individuals [69]. Leptin is a hormone secreted by adipocytes and is involved with energy homeostasis, namely through its ability to cross the blood brain barrier to decrease orexigenic neuropeptides and increase anorexigenic neuropeptides [70]. In healthy individuals, leptin is secreted in proportion adipose tissue and energy intake [71]. Leptin is generally thought of as a satiety hormone, although many obese individuals have "leptin resistance" [72] where the secretion of leptin in these individuals does not suppress appetite or lead to reduced energy intake.

The role of leptin may extend beyond energy homeostasis. BMI and plasma leptin levels in OA patients correlate positively [70]. Plasma leptin concentrations have also been found to be 3 times higher in premenopausal women than men [73]. Bao et al. [74] found that injecting the knee with leptin caused significant degradation of the cartilage. Additionally, leptin taken from the synovial joint has been found to be higher than plasma leptin concentrations [75].

Results from our research group, corroborates previous findings [76]. In this study, we examined the relationship between serum and synovial fluid concentrations of leptin in both males and females with varying degrees of OA. Serum and synovial fluid samples were obtained from 20 men (mean age = 68.4 ± 10.8 years) and 20 women (mean age = 61.6 ± 12.4 years) with varying degrees of OA who underwent arthroscopic or total knee replacement surgery. We found that leptin concentrations in both the serum and synovial fluid of patients with knee OA increased according to disease severity. That is, as the level of OA became more severe, the leptin concentration also increased, in both men (**Figure 3A**) and women (**Figure 3B**). We also found a significant correlation between serum and synovial fluid leptin concentration and BMI in both men (**Figure 4A** and **B**) and women (**Figure 5A** and **B**) with OA. These findings indicate that leptin may in part play a role in the increased risk of OA related to obesity.

The mechanism by which leptin may contribute to the pathophysiology of OA is likely due to its place in the cytokine family [72]. Leptin may trigger immune responses by increasing the expression of adhesion molecules, likely through a pro-inflammatory cytokine pathway [77]. Additionally, mice without a working leptin gene (ob/ob) demonstrated decreased secretion of inflammatory cytokines, while the administration of leptin to these mice restored inflammatory secretions [78]. Additionally, leptin receptors are present in the cartilage suggesting a direct action on this tissue. There is evidence [79] that leptin stimulates inflammatory markers Interlukin-6 (IL-6), Interlukin-8 (IL-8), nitric oxide, Interlukin-1 β (IL-1β), Tumor Necrosis Factor-alpha (TNFα), COX2, and PGE 2 in the joint thereby contributing to cartilage matrix breakdown.

Because of isoflavones' role in inflammation, the negative action of excess leptin levels on cartilage may be suppressed by isoflavones. For example, rats fed a high fat

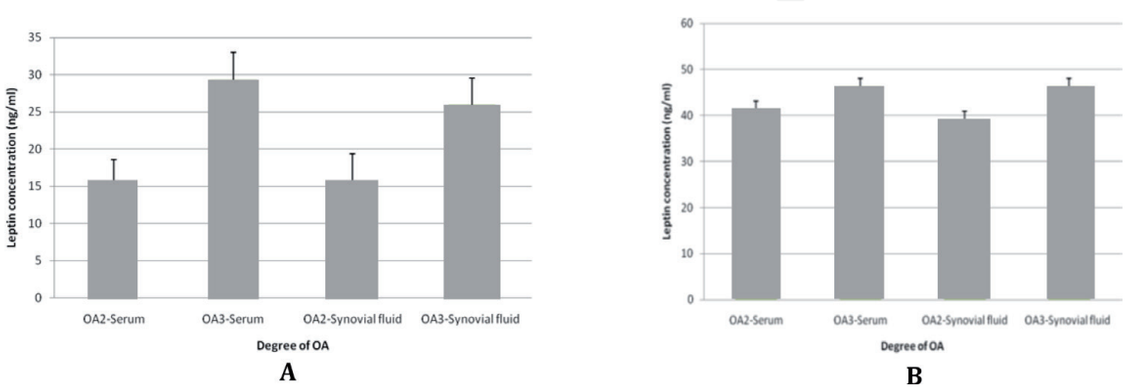

Figure 3.
The relationship between serum and synovial fluid concentrations of leptin and severity of OA in both men (A) and women (B).

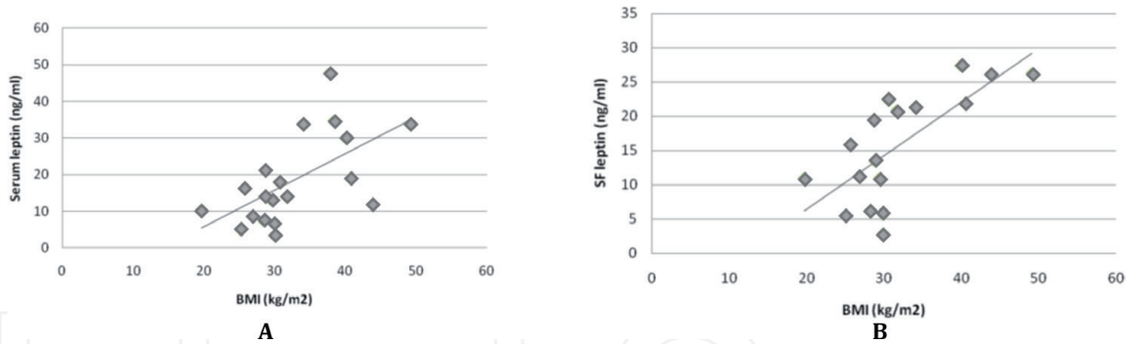

Figure 4.
The correlation between serum (A) and synovial fluid (B) leptin concentration and BMI in men with OA.

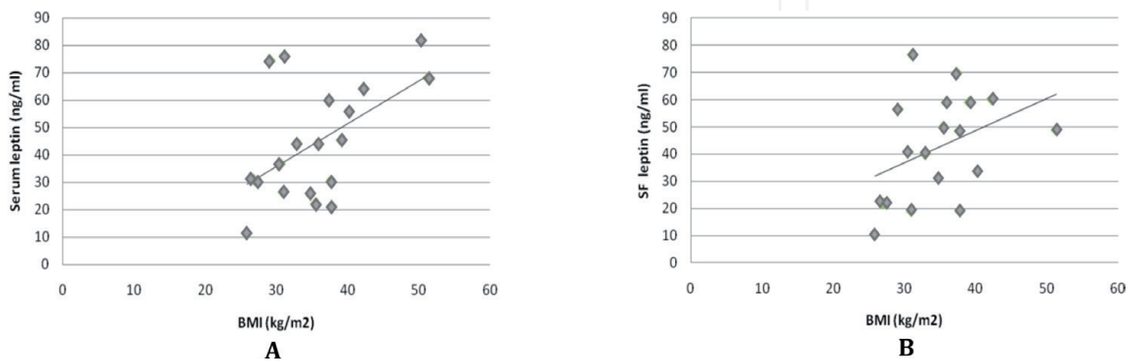

Figure 5.
The correlation between serum (A) and synovial fluid (B) leptin concentration and BMI in women with OA.

soy diet, or regular soy diet, were found to have lower serum leptin concentrations than those fed a high fat casein, or regular fat casein diet [80]. Their study [80] also found that the expression of inflammatory genes decreased along with the expression of leptin. Niwa et al. [81] also found that soy isoflavones decreased leptin secretion in the adipocytes of mice, and a study by Llaneza et al. [82] found that the consumption of 200 mg of soy isoflavone extract in postmenopausal women resulted in decreased leptin levels, as well as TNFα. Another study in overweight and obese subjects found that after 12 weeks of black soy peptide supplementation, serum leptin concentrations were significantly reduced from baseline [83].

These studies and our observations so far suggest that soy and its isoflavones are likely very efficacious in alleviating pain associated with OA and its symptoms, in part due to its ability to decrease inflammatory responses. Soy's ability to mediate leptin and inflammatory immune responses may also be integral in both preventing OA, halting its progression, and improving the QOL of individuals affected.

6. Soy and OA

The main soy isoflavones include genistein, daidzein, and glycetine [84]. Genistein is structurally similar to ipriflavone [84], a synthetic isoflavone. SERMs such as tamoxifen [85] and ipriflavone [86] have both been shown to influence cartilage metabolism and reduce or alleviate the symptoms associated with OA. Therefore, it is conceivable to also expect that genistein similarly influences cartilage metabolism.

Our *in vitro* study [87] found that genistein had the capacity to reduce inflammation in human chondrocytes. Indeed, in chondrocytes treated with LPS to induce inflammation, genistein significantly decreased COX-2 production (**Figure 6**), but

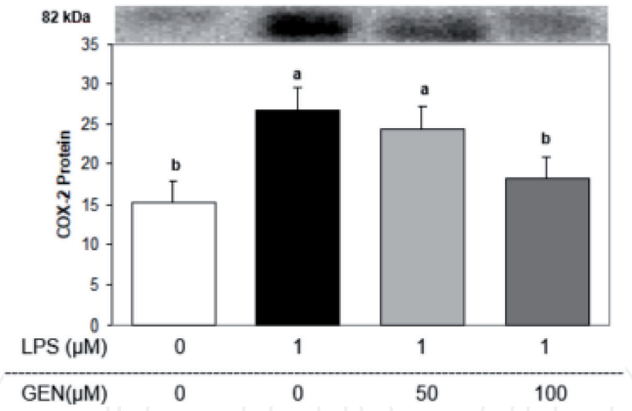

Figure 6.
COX-2 levels in cytosolic fraction of chondrocytes. LPS, lipopolysaccharides; and GEN, genistein. Bars represent mean ± SE, n = 3 per treatment group. Bars with different letters are significantly different from each other (P < 0.05).

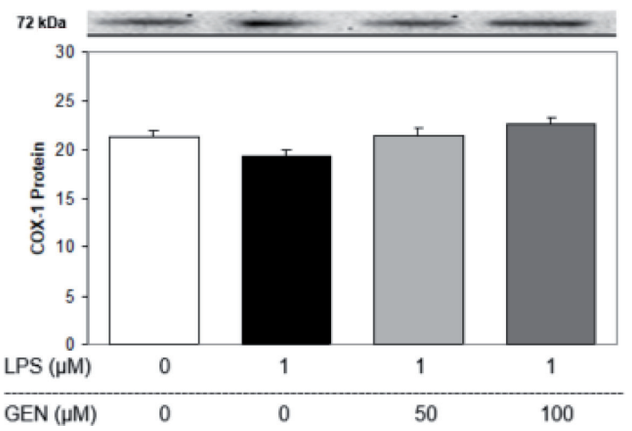

Figure 7.
COX-1 levels in cytosolic fraction of chondrocytes. LPS, lipopolysaccharides; and GEN, genistein. Bars represent mean ± SE, n = 3 per treatment group.

did not have an effect on COX-1 production (**Figure 7**) [87]. This is of particular interest, as NSAIDs are thought to inhibit inflammation via COX-1 and COX-2 dependent pathways, but are thought to cause damage because of the inhibition of COX-1, an important enzyme that regulates normal cellular processes and is expressed in most tissues [88]. This inhibited synthesis caused by most NSAIDS can negatively affect the maintenance and integrity of the gastric and duodenal mucosa, as well as lead to kidney issues [89, 90]. COX-2, however, is generally unexpressed by most tissues and is upregulated specifically by inflammation [91]. The seemingly selective inhibition of COX-2 by genistein provides a promising alternative to those who experience gastric distress due to the use of NSAIDs.

IL-1β, an inflammatory cytokine, was also measured in this study and was found to be lower in both the high and low doses of genistein (**Figure 8**) [87]. More importantly, YKL-40, a marker of human cartilage glycoprotein degradation [92], was found to be suppressed in genistein treated groups (**Figure 9**); however, the difference between the LPS and genistein groups did not reach statistical significance [87].

An animal study by Borzan et al. [93] also supports our clinical findings on soy. The aim of the aforementioned study was to determine if a soy diet could reduce the pain behaviors and inflammation induced by the intraplantar administration of complete Freund's adjuvant. They reported that neuropathic pain following partial sciatic nerve injury was attenuated in rats fed a soy protein diet [93], indicating that soy may be effective in attenuating pain symptoms, including those of OA.

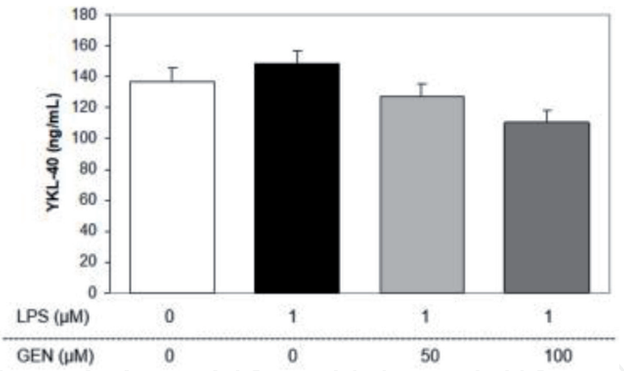

Figure 8.
IL-1β level in culture supernatant measured via ELISA kit. LPS, lipopolysaccharides; and GEN, genistein. Bars represent mean ± SE, n = 4 per treatment group.

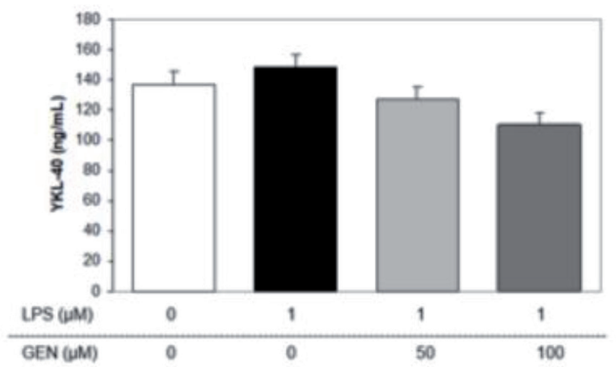

Figure 9.
YKL-40 level in culture supernatant which was measured via ELISA kit. LPS, lipopolysaccharides; and GEN, genistein. Bars represent mean ± SE, n = 4 per treatment group.

Lymphocytes and monocytes are often seen at sites of injury and inflammation [51]. Our lab investigated the effect of soy isoflavone supplementation on ovariectomy induced lymphopoiesis in rats. In this animal study [94], we observed that ovariectomy-induced increases in peripheral blood total lymphocyte and monocyte counts were returned to the levels of sham-operated rats after soy isoflavone supplementation (**Figure 10A** and **B**). Forty-eight 12-month-old Sprague-Dawley rats were either sham-operated (sham; 1 group) or OVX (3 groups) and were fed a standard semi-purified diet for 120 days. Thereafter, the OVX groups received one of the three doses of isoflavones: 0 (OVX), 500 (ISO500), or 1000 (ISO1000) mg/kg diet for 100 days. Ovariectomy significantly ($P < 0.05$) increased the total leukocyte, lymphocyte, monocyte, eosinophil, and basophil counts. Isoflavones at 500 and 1000 mg/kg diet returned the total leukocyte counts as well as leukocyte subpopulations to levels comparable to that of sham. These findings indicate that isoflavones are capable of normalizing circulating levels of inflammatory cells that produce many proinflammatory mediators, which may prove effective for the synovial joint.

Our lab also carried out a three-month double-blind randomized clinical trial [95] to investigate the effects of soy supplementation on symptoms associated with knee OA. About 135 free-living individuals (64 men, mean age = 55.8 ± 13.6 years; and 71 women, mean age = 59.3 ± 12.0 years) with knee OA were randomly assigned to receive 40 g of either soy protein or milk protein daily. This study indicated that soy protein regimen containing 88 mg isoflavones improved ($P < 0.05$) knee range of motion and ability to climb several flights of stairs, and reduced ($P < 0.05$) the intensity, frequency, severity of pain, hindrance to activities (**Figure 11A**), and use of pain medications (**Figure 11B**). The improvement in self-described pain parameters

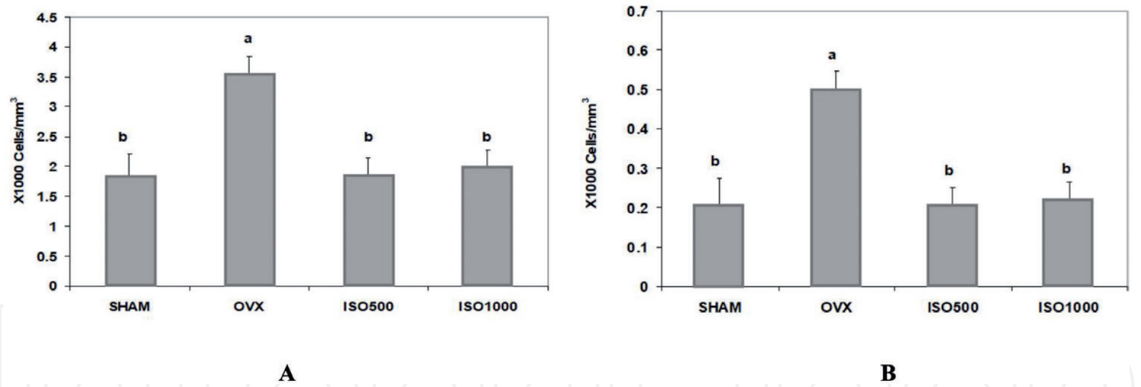

Figure 10.
(A and B) Indicate effects of isoflavones (ISO) on lymphocyte and monocyte counts. Values are mean ± SE (n = 12). Bars that do not share the same superscript are significantly different (P < 0.05).

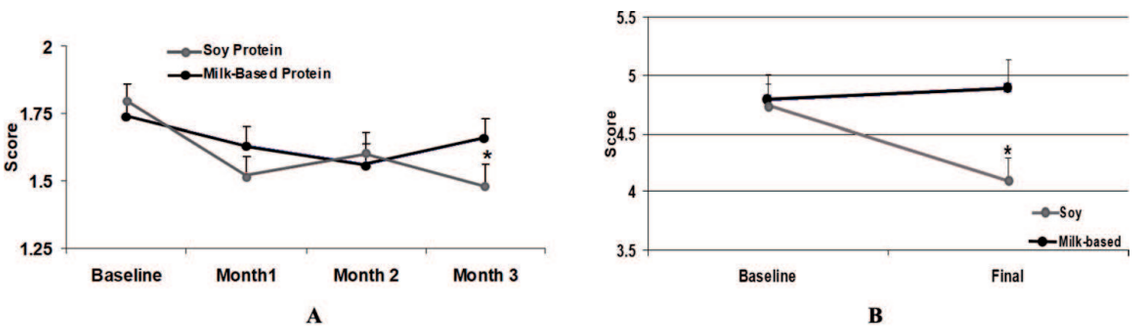

Figure 11.
(A) represents self-reported pain limiting physical activities with scores ranging from 1 to 2; (1) referring to no limitation and (2) referring to pain as causing limitation in physical activity. (B) indicates the use of pain medications (mean + SE). A lower score reflects less use of pain medication and a higher score reflects more frequent use of pain medication.

due to soy supplementation became more pronounced as the treatment duration progressed. Additionally, the soy regimen significantly improved circulating levels of IGF-I which suggests that isoflavones may exert anabolic effects on the cartilage.

In the same study, serum IGF-I as well as human cartilage glycoprotein 39 (YKL-40), a marker of joint destruction [92], were assessed. Results indicated that protein supplementation had significantly lowered mean serum concentration of YKL-40 in men, implying that soy can slow down cartilage degradation. Although both proteins, as expected, increased ($P < 0.05$) circulating levels of IGF-I, soy protein had a more pronounced effect compared to milk protein. We have repeatedly shown [84, 96] that soy has the ability to uniquely enhance serum IGF-I in comparison with milk protein, indicating that this effect may be due to its isoflavone content rather than merely protein.

The findings of our three-month study indicate that soy protein supplementation significantly reduced the intensity and frequency of pain. By comparison, milk protein only reduced pain intensity indicating that the reduction in the frequency of pain and discomfort are specific to soy and not the control protein. Our findings also indicate a reduced need for pain medication. The increased serum IGF-I level with soy supplementation suggests that isoflavones may exert anabolic effects on the cartilage, and decreased YKL-40 levels which is associated with cartilage degeneration, support our hypothesis that soy can improve symptoms and severity of OA. The authors suggest that people with no contraindications to soy isoflavones use ipriflavone, a synthetic isoflavone, for decreasing the symptoms of OA. However, this is just a suggestion and further research must be done to assess the potency of isoflavone usage for symptomatic control of OA.

7. Soy and cardiovascular disease

As mentioned previously, soy isoflavones are phytoestrogens. Estrogen is known to be cardioprotective, so it stands to reason that soy may also be cardioprotective. Many of the clinical trials investigating the effect of soy supplementation on heart health focus mainly on cholesterol levels. This may be due to the fact that the phytosterols, like those found in soy, compete with cholesterol for intestinal absorption [97]. A 2015 study [98] investigated the effect of 8 weeks of standard soymilk supplementation against the effect of 2 g/day of phytosterols and 10 g/day of inulin-enriched soymilk supplementation. While both groups did see a reduction in LDL-C in both groups, the study group supplementing with the extra phytosterols and inulin saw significantly better results. TC was also significantly reduced in the study group, compared to the control of regular soymilk.

Soy can be beneficial in many forms beyond that of soymilk. A study [99] that supplemented whole soy foods (3–4 servings per day) for 12 weeks found that the soy intervention significantly reduced total cholesterol, LDL-C, non-HDL cholesterol, and apoB even though BMI did not decrease. An earlier study [100] also found that soy protein supplementation resulted in decreased cholesterol levels. Prehypertensive women who supplemented 40 g of soy flour saw decreases in LDL-C and well as high sensitivity C-Reactive Protein (CRP), a marker of inflammation [101]. Interestingly, another study found that 1 month of soy nut supplementation modestly reduced arterial stiffness but did not improve inflammatory biomarkers [102]. Additionally, Lucas et al. [103] found that soy isoflavones prevented both hyperlipidemia and atherosclerotic lesions in ovariectomized Golden Syrian Hamsters.

While there are still gaps in the research for CVD and soy consumption, research generally points to a positive effect of soy on heart health, irrespective to its effect on cholesterol. Finding that soy significantly decreased the development of atherosclerotic lesion in a hamster model of postmenopausal CVD is particularly important since CVD remains the leading cause of death in the US.

8. Soy and osteoporosis

Just as OA greatly affects women more so than men, osteoporosis is a particularly concerning problem for the aging female population. Because intestinal cells contain ER, and because estrogen enhances calcium transport [104], it stands to reason that phytoestrogens like soy may increase intestinal calcium transport. There have been multiple studies researching intestinal transport of calcium and soy, as well as the effect of soy on animal models of osteoporosis, and human studies. A study by our lab in 2001 [104] confirmed that not only does ovariectomy decrease rates of calcium transport, but that soy isoflavones in soy protein promoted calcium absorption in a manner analogous to estrogen without any of the side effects/risk. Pawlowski et al. [105] also found that soy isoflavones were effective in increasing calcium retention in bone, and Arjmandi et al. [84] found that women not on hormone replacement therapy who supplemented soy protein experienced reduced urinary calcium excretion.

Animal studies have yielded positive results for isoflavone's bone sparing properties. A 1998 study [106] by our lab compared casein protein and soy protein in ovariectomized (OVX) rats, and found that soy protein with higher levels of isoflavones spared the femoral bone density decreases brought about by ovariectomy. Our 2006 study [107] found that soy positively affected tibial architectural properties of OVX rats, including trabecular thickness, separation, and number

without preserving BMD. Another study by our lab [108] found that soy protein with or without isoflavones did not preserve BMD in a male rat model of osteoporosis, but did positively affect the biomechanical properties of bone including yield and ultimate force which are measures of elasticity and plasticity in bone. Multiple other studies have concluded that any bone sparing effects of soy consumption are likely due to soy isoflavone content, which increases bone formation and improves the architectural properties of bone [109–112].

Interestingly, while animal studies have been promising for moderate prevention of bone loss, a 2-year Thai study [113] found that soy isoflavones did not significantly reduce bone loss. Similarly, a 3-year study [114] that gave postmenopausal women soy isoflavones did not find significant bone sparing effects, except for the femoral neck which was still only modestly affected by supplementation. The same lab then evaluated the safety of soy isoflavone supplementation by evaluating effects on hormones, endometrial thickness, and any adverse events, finding no negative evidence of treatment effect on this population, once again indicating that soy supplementation is safe. Wong et al. [115] found that 120 mg of soy isoflavones did reduce whole body BMD loss, but did not positively affect common female fracture sites. Studies by our lab [96, 116], and others [117], generally find that soy supplementation for the treatment of osteoporosis generally has little to no effect on BMD, but may still positively affect bone metabolism as well as bone quality.

9. Conclusions and future directions

Although the role of soy in CVD, lowering cholesterol, and improving bone has been questioned, there is ample evidence to suggest that soy improves symptoms of OA by at least three mechanisms, including (1) acting as a SERM, thereby modulating estrogen receptors; (2) increasing circulating levels of IGF-1, thereby regenerating cartilage and/or preventing further damage; (3) and inhibiting production of inflammatory molecules, such as COX-2, TNF-α. The authors believe that soy plays an important role in the healthy aging process by decreasing the incidence of OA, and allowing those who are afflicted to achieve greater mobility, thus decreasing their chances of developing other chronic diseases that would have resulted from decreased mobility. Therefore, we suggest that consumption of soy and soy isoflavones is crucial for healthy aging and improved QOL throughout the aging process.

We have demonstrated that both leptin and estrogen have a significant role in the etiology, progression, and treatment of OA, but the specifics of that role remain uncertain. The above studies also indicate a positive effect of soy supplementation on cartilage metabolism, inflammation, and indices of pain, likely through the modulation of the aforementioned factors. Soy appears to be promising in the treatment of OA symptoms, but its ability to prevent the disease is questionable. While isoflavones are known to act as SERMs, it is reasonable to suspect that the protein content of soy as a whole in conjunction with isoflavone content is responsible for positive effects in this population. Though the literature indicates that soy supplementation may be helpful in decreasing usage of NSAIDs, slow cartilage degradation, and increase functionality in individuals afflicted with OA, determining the safety as well as the efficacy of soy or its isoflavones as a long-term OA intervention is the next logical step. Any intervention that can improve the QOL of individuals afflicted with OA is worth pursuing, but it is paramount that researchers uncover the exact etiology of the disease so as to prevent future occurrences.

The literature referenced here also indicates that soy can be promising for other chronic disease states, without necessarily posing a risk for increased instance of breast cancer. However, there is still much confusion about which populations are

at higher risk for breast cancer when consuming soy. The multiple health benefits appear to outweigh breast cancer risk for most women, even decreasing the chance of breast cancer, but further interventional, rather than strictly epidemiological and cell culture studies, need to be established.

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Conflict of interest

The authors have no conflict of interest to declare.

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