

*Review*

## **Nutraceuticals: Potential for Chondroprotection and Molecular Targeting of Osteoarthritis**

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**Abstract:** Osteoarthritis (OA) is a degenerative joint disease and a leading cause of adult disability. There is no cure for OA, and no effective treatments which arrest or slow its progression. Current pharmacologic treatments such as analgesics may improve pain relief but do not alter OA disease progression. Prolonged consumption of these drugs can result in severe adverse effects. Given the nature of OA, life-long treatment will likely be required to arrest or slow its progression. Consequently, there is an urgent need for OA disease-modifying therapies which also improve symptoms and are safe for clinical use over long periods of time. Nutraceuticals—food or food products that provide medical or health benefits, including the prevention and/or treatment of a disease—offer not only favorable safety profiles, but may exert disease- and symptom-modification effects in OA. Forty-seven percent of OA patients use alternative medications, including nutraceuticals. This review will overview the efficacy and mechanism of action of commonly used nutraceuticals, discuss recent experimental and clinical data on the effects of select nutraceuticals, such as phytoflavonoids, polyphenols, and bioflavonoids on OA, and highlight their known molecular actions and limitations of their current use. We will conclude with a proposed novel nutraceutical-based molecular targeting strategy for chondroprotection and OA treatment.

**Keywords:** nutraceuticals; osteoarthritis; molecular targets

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## 1. Introduction

Osteoarthritis (OA) affects over 27 million Americans, is a leading cause of pain and disability [1,2], and is a significant economic burden in the United States, with over \$185.5 billion in annual medical care expenditure [3]. OA is a disease of the entire synovial joint, and affects the underlying bone, synovium, meniscus, ligaments/tendons, and articular cartilage [4,5]. Progressive degradation and eventual loss of articular cartilage is the pathological hallmark of osteoarthritis, and is a major target for exploring disease-modifying treatment [4,6–8]. Cartilage plays a major role in cushioning the ends of the bones, allowing for the articulation of opposing joint surfaces. Destruction of articular cartilage leads to bones rubbing against each other, causing stiffness, pain, and ultimately, loss of movement in the joints [9].

There is currently no cure for OA, and there are no therapies which slow or arrest OA progression [6,10]. So far, most treatments primarily focus on the secondary effects of the disease, such as relieving pain and improving joint function, but fail to address the evolving and complex nature of OA. For example, analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), which are commonly prescribed to OA patients, generally decrease pain and improve function, but have no demonstrated beneficial effect on chondroprotection or OA disease prevention and modification [11]. Furthermore, long-term use of available pharmacological agents to relieve OA symptoms is associated with substantial gastrointestinal, renal, and cardiovascular side effects [11,12]. Given the nature of OA, life-long treatment will likely be required to arrest or slow its progression. Consequently, there is an urgent need for OA disease-modifying therapies, which in the best case scenario also improve symptoms, and are safe for clinical use over long periods of time.

Nutraceuticals—food or food products that provide medical or health benefits, including the prevention and/or treatment of a disease—offer not only a safe alternative to current pharmacologic therapies, but may exert disease- and symptom-modification effects in OA [13]. Forty-seven percent of adults use non-prescribed alternative medications (including food supplements and nutraceuticals) for OA management [14]. Recent studies indicate phytoflavonoids, polyphenols, and bioflavonoids, which are natural compounds found in fruits, teas, spices, wine, and vegetables, have shown the most potential to modify OA disease and symptoms based on their anti-inflammatory and anti-catabolic actions, and protective effects against oxidative stress [15]. In this review, we will summarize the clinical effects and potential mechanisms of action of commonly used nutraceuticals for OA treatment. We will then focus on nutraceuticals such as phytoflavonoids, polyphenols, and bioflavonoids, which have strong *in vitro* and pre-clinical evidence for treating OA, but are not well studied in clinical trials. The review will conclude with a novel nutraceutical-based targeting approach which may be utilized to effectively prevent OA initiation or arrest or slow OA progression.

## 2. Efficacy and Mechanism of Action of Currently Used Nutraceuticals

Nutritional agents, which offer favorable safety profiles, have long-generated interest for their potential in disease modification. Dietary macronutrients, including proteins and amino acids, fatty acids (e.g., omega-3), vitamins, and certain minerals not only provide building blocks for biological processes, but have the potential to support and influence the structure and function of joints [16–18]. For example, increased consumption of Vitamin C, an antioxidant vitamin found in many fruits and vegetables, was associated with reduced risk of cartilage loss and OA progression for OA patients [19]. Conversely, not eating “healthy foods,” including those that are high in fat and sugar, may exacerbate the disease [18,20]. Collectively, ingredients in foods are essential for joint health and certain ingredients have a critical impact on altering OA initiation and progression. Nutraceuticals including herbal medicines such as *Boswellia serrata*, *Harpogophytum procumbens*, *Phytodolor*, Willow bark, and supplements such as Green-lipped mussel, glucosamines, chondroitin, collagen hydrolysate, lipids (avocado/soybean unsaponifiables), and essential fatty acids, are used for OA (Table 1). In particular, glucosamine and chondroitin sulphate are among the most common nutraceuticals used for the treatment of OA. Glucosamine, an aminosaccharide initially isolated from the chitin of shellfish, is an important component of glycosaminoglycan chains and the production of proteoglycans, a major cartilage extracellular matrix protein [21]. Chondroitin sulphate is a glycosaminoglycan used in the synthesis of proteoglycans [22]. Despite the large number of studies examining the efficacy of glucosamine, chondroitin sulphate, or the two in combination for the treatment of OA, studies tend to show that these drugs result in little improvement compared with placebo in both symptomatic and structural outcomes [23–25]. These clinical trial findings may be due to the complexity and challenge of OA treatment, in addition to the effectiveness of dose, route of administration, and quality of the various products. Furthermore, clearly understanding the mechanism of action of glucosamine and chondroitin sulfate may provide better guidance for clinical use.

**Table 1.** Clinical efficacy and mechanisms of action of commonly used nutraceuticals for osteoarthritis (OA).

Herbal/Plant-based extracts and medicines		
Nutraceuticals	Clinical efficacy	Mechanisms of action
<i>Boswellia serrata</i>	Relieved joint pain, reduced joint swelling and stiffness, increased joint flexion and walking distance [26–28]	Inhibited TNF- $\alpha$ -induced MMP-3 expression and protected against IL-1 $\beta$ -induced chondrocyte death [29]
Bromelain (pineapple extract)	Did not significantly relieve pain or quality-of-life symptoms [30]	Decreases PGE <sub>2</sub> expression [31]
<i>Caesalpinia Sappan</i> extract (CSE)	Not reported	Inhibited inflammatory mediators IL-1 $\beta$ , iNOS, COX-2 and TNF- $\alpha$ expression in IL-1 $\beta$ stimulated primary human chondrocytes [32]. CSE also suppressed <i>MMP-1</i> , <i>MMP-3</i> , <i>MMP-7</i> , <i>MMP-9</i> and <i>MMP-13</i> gene expression [33]

Table 1. Cont.

Herbal/Plant-based extracts and medicines		
Nutraceuticals	Clinical efficacy	Mechanisms of action
Capsaicin	Reduced pain and stiffness and increased joint function [34–36]	Agonist for transient receptor potential vanilloid 1 (pain receptor); Prolonged exposure of capsaicin leads to desensitization of this pain pathway [37]
Cat's claw	Reduced OA-associated pain [38,39]	Inhibit lipopolysaccharide (LPS)-induced PGE <sub>2</sub> production and activation of TNF- $\alpha$ [38]
Chicory root	Improved pain and relieved joint stiffness [40]	Inhibits production of COX-2, iNOS, TNF- $\alpha$ , and NF- $\kappa$ B [41,42]
<i>Diallyl sulphide</i> (garlic extract)	Not reported	Inhibited IL-1 $\beta$ -induced expression of MMP-1, -3 and -13. Ameliorated OA in rabbit anterior cruciate ligament transaction mode and reduced MMP-1, -3, -13 [43]; Inhibited COX-2 expression induced by IL-1 $\beta$ [44]
Duhuo Jisheng Tang	Reduced pain and stiffness as well as improved physical function in OA patients [45]	Not reported
<i>Harpogophytum procumbens</i> (Devil's claw)	Alleviates pain in OA patients [46–48]	Inhibited release of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and PGE <sub>2</sub> [49]
<i>Phyllanthus emblica</i>	Not reported	Inhibited hyaluronidase and type II collagenase activities <i>in vitro</i> and reduced GAG release in cartilage explants from OA patients [50].
Willow bark	Reduced OA-related pain [51,52]	Not reported
Supplements		
Nutraceuticals	Clinical efficacy	Mechanisms of action
Aloe Vera	Protects against gastrointestinal effects of NSAIDs [53]	Not reported
Avocado/soybean unsaponifiables	Reduced pain in OA patients and reduced NSAID consumption [54,55]	Reduced levels of iNOS and MMP-13 [56]. Suppressed TNF- $\alpha$ , IL-1 $\beta$ , COX-2, and iNOS in LPS-activated chondrocytes [57]
Calcium Fructoborate	Not reported	Suppresses IL-1 $\beta$ , IL-6, iNOS <i>in vivo</i> [58]
Collagen hydrolysates	Alleviates OA-related pain [59,60]	Stimulate regeneration of type II collagen and increases biosynthesis of proteoglycans [59]
Edible Bird's nest extract	Not reported	Reduced gene expression of MMP-1, MMP-3, IL-1, IL-6, IL-8, COX-2, PGE <sub>2</sub> , and iNOS and increased type II collagen, aggrecan and SOX-9 [61]
Genistein	Not reported	Reduces IL-1 $\beta$ and COX-2 protein synthesis in LPS-induced human chondrocytes [62].

Table 1. Cont.

Herbal/Plant-based extracts and medicines		
Nutraceuticals	Clinical efficacy	Mechanisms of action
Green-Lipped Mussel extract	Improved knee joint pain, stiffness and mobility [63]	Inhibits synthesis of pro-inflammatory molecule Leukotriene B4 and production of PGE2 [64]
Lactobacillus casei	Not reported	Decreased TNF- $\alpha$ , IL-6, NF- $\kappa$ B, COX-2, MMP-1, -3, -13 and increased IL-4 and IL-10 [65]
Methylsulfonylmethane (MSM)	Improved symptoms of pain and physical function [66]	Scavenge hydroxyl free radicals [67]; sulfur content rectifies dietary deficiencies of sulfur to improve cartilage formation [68]
Polyunsaturated fatty acids (PUFA)	High levels of N-3 PUFA associated with less cartilage loss [69]	N-3 PUFA abolished TNF- $\alpha$ , IL-1 $\beta$ , COX-2, MMP-3, -13, ADAMTS5 expression <i>in vitro</i> [70] and protected against cartilage degradation in OA prone animals [71]
S-adenosylmethionine	Reduced OA-related pain intensity from baseline [72–74]	Increases proteoglycan synthesis [75] and chondrocyte proliferation [76]
Vitamins		
Nutraceuticals	Clinical efficacy	Mechanisms of action
Niacinamide (B-complex vitamins)	Improved joint mobility [77]	Not reported
Vitamin C		Stimulates collagen and proteoglycan synthesis [78]
Vitamin D	No effect on pain severity or MRI-assessed quantitative cartilage loss [79]; Relieved OA-associated joint pain [80]	Not reported
Vitamin E	Relieved OA-related pain and improved physical function [81,82]	Not reported

Not reported: based on Pubmed search on 9/15/2013.

### 3. Pre-Clinical and Clinical Effects of Phytoflavonoids, Polyphenols, and Bioflavonoids Nutraceuticals on OA

Recent studies suggest that nutraceutical compounds such as phytoflavonoids, polyphenols, and bioflavonoids, derived from green tea, pomegranate, ginger, turmeric and rose hips, have shown promising preliminary evidence for their chondroprotective effect in OA prevention and treatment (Table 2).

**Table 2.** The actions of select phytoflavonoids, polyphenols, and bioflavonoids nutraceuticals on arthritis.

Nutraceutical	Clinical effects	Preclinical effects
Green tea	Not reported	<ul style="list-style-type: none"> <li>• Lowered arthritis incidence and index score in collagen-induced arthritis [83]</li> <li>• Decreased inflammatory mediators TNF-<math>\alpha</math>, COX-2 [83]</li> <li>• Reduced serum levels of IL-17, and increased serum levels of IL-10 [84]</li> </ul>
Pomegranate	Not reported	<ul style="list-style-type: none"> <li>• Reduced cartilage damage and proteoglycan loss in OA mice [85]</li> </ul>
Ginger	<ul style="list-style-type: none"> <li>• No difference between ginger- and placebo-treated groups in OA patients after 3 weeks [86]</li> <li>• Improved pain in OA patients after 6 weeks [87]</li> </ul>	Not reported
Tumeric	<ul style="list-style-type: none"> <li>• Improvement in pain and mobility [88]</li> </ul>	Not reported
Rosehip powder	<ul style="list-style-type: none"> <li>• Reduced OA-associated pain [89]</li> </ul>	Not reported

### 3.1. Green Tea

Green tea is one of the most commonly consumed beverages in the world and is a rich source of polyphenols including epigallocatechin 3-gallate (EGCG) [90]. EGCG has strong anti-oxidant activity, up to 25–100 times more potent than Vitamin C and E [91]. The efficacy of EGCG or green tea extracts in human arthritis has yet to be tested, but there is strong evidence in small animal studies for advancing green tea-based therapies toward clinical application.

EGCG administered to collagen-induced arthritis mice, an inflammatory model of arthritis, via drinking water, lowered arthritis incidence and slowed progression of disease [83]. This disease-modifying effect was associated with a decrease in inflammatory mediators TNF- $\alpha$ , COX-2, and lower levels of total immunoglobulins (IgG) and type II collagen-specific IgG levels, indicating a reduced inflammatory immune response [83]. Daily administration of green tea extracts in drinking water slowed progression of arthritis in rat adjuvant-induced arthritis, inhibited serum levels of IL-17, and increased serum levels of IL-10 [92]. As cartilage destruction is a hallmark of both OA and RA, and inflammation also plays a role in OA, albeit to a lesser extent than in RA, green tea extracts may exert a good potential for OA prevention and treatment.

### 3.2. Pomegranate

Pomegranate fruit is used in traditional medicines to treat inflammation and pain in diseases including arthritis [90]. Pomegranates are considered to have strong anti-oxidant properties due to their high content of soluble polyphenols hydrolyzable tannin and punicalagin [93]. Pomegranate is also rich in anthocyanins, a polyphenolic compound that exhibits anti-oxidant and anti-inflammatory capabilities [94]. In the mono-iodoacetate OA mouse model, pomegranate juice administered by oral

gavage for two weeks significantly reduced cartilage damage and proteoglycan loss, especially in the groups receiving the higher doses [85]. This study provides some *in vivo* evidence that pomegranate juice may improve the joint pathology in OA.

### 3.3. Ginger

Ginger is a widely used condiment and has long been prescribed in China and India for conditions such as nausea, vomiting, headaches, and arthritis, due to its anti-inflammatory and circulatory stimulant effects [95,96]. Ginger is non-toxic and is generally recognized as safe by the United States Food and Drug Administration. As an alternative to NSAID therapy for arthritic conditions, ginger has shown moderately positive results [97]. A randomized, placebo-controlled, crossover study comparing ginger extracts and ibuprofen was performed and the study revealed significant improvement in symptoms for both groups before crossover. After the crossover, no difference was noted between the ginger- and placebo-treated groups [86]. A randomized, double-blind, placebo-controlled trial also studied the effects of ginger and galangal extracts, a spice that is closely related to ginger, in the treatment of knee OA. OA patients treated with ginger and galangal extracts showed greater improvement in pain compared to the placebo group [87].

### 3.4. Turmeric

Turmeric is a widely used spice and is generally regarded as safe [98]. The major component of turmeric is curcumin, which constitutes up to 90% of total curcuminoid content. Although curcumin has been demonstrated to exert potent anti-inflammatory effects *in vitro*, there is no clinical data available for the effect of curcumin in OA treatment [19]. However, OA patients treated with a formulation containing curcumin exhibited positive results in pain management and mobility compared to the placebo control [88].

### 3.5. Rosehip Powder

Rosehip powder is extracted from fruits of the rose plant, and has been used extensively in traditional medicine [99]. A meta-analysis of randomized controlled trials (RCTs) showed rosehip powder reduced pain and led to reduced use of analgesics in OA patients [89]. A longer-term clinical trial comparing different rosehip formulations in patients with knee OA is currently undergoing (Clinical trial NCT01430481).

## 4. Nutraceuticals for Molecular Targeting of OA

### 4.1. Molecules in Pathology of OA Initiation and Progression

Chondrocytes, the sole cell population within the articular cartilage, are primarily responsible for the maintenance of the extracellular matrix [100]. In healthy adult cartilage, chondrocytes are normally quiescent. However, in OA, chondrocytes undergo phenotypic alterations, which include abnormal proliferation, cell death, senescence, and significant changes in gene expression, such as increased

expression of inflammatory cytokines, matrix proteins and proteolytic enzymes [4,101]. Together, these lead to a loss of homeostatic balance of the articular cartilage and osteoarthritis.

In the early stages of OA, many inflammatory mediators are expressed in the cartilage and synovial tissue, which contribute to the progression of the disease [102–104]. Increased inflammation is the consequence of many factors, including mechanical overloading, joint injury, adipose tissue, and cartilage matrix fragments [105,106]. Interleukin (IL)-1 $\beta$  and tumor necrosis factor (TNF)- $\alpha$  are considered the most prominent pro-inflammatory cytokines involved in OA [104]. Elevated levels of both IL-1 $\beta$  and TNF- $\alpha$  are found in OA joint tissues, including the articular cartilage, subchondral bone, synovial fluid and synovium [107]. IL-1 $\beta$  and TNF- $\alpha$  alter the homeostatic balance of chondrocytes by suppressing anabolic activity, stimulating catabolic breakdown of the articular cartilage, and increasing production of inflammatory mediators and reactive oxygen species (ROS). These effects of IL-1 $\beta$  and TNF- $\alpha$  are mediated, at least in part, by members of the mitogen-activated protein kinases (MAPK), nuclear factor-kappa (NF- $\kappa$ ) B transcription factors, and certain members of the Wnt- $\beta$ -catenin signaling pathways [108–110]. IL-1 $\beta$  and TNF- $\alpha$  suppress expression of major structural components in the articular cartilage, including type II collagen and proteoglycans [111–114]. IL-1 $\beta$  and TNF- $\alpha$  also increase expression of proteolytic enzymes which directly cleave the cartilage matrix, including matrix metalloproteinases (MMPs)-1, -3, -13, and ADAMTS (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs) [115–117]. Furthermore, IL-1 $\beta$  and TNF- $\alpha$  stimulate production of inflammatory mediators prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) and cyclooxygenase 2 (COX-2), and ROS including nitric oxide (NO) and the superoxide anion [104,118].

Since the above-mentioned pro-inflammatory cytokines, inflammatory mediators, and proteolytic enzymes play critical roles in OA initiation and progression, these molecules have been targeted for OA treatment. Treatments against IL-1, such as Anakinra, a modified form of native IL-1Ra, have demonstrated chondroprotection in an animal model of OA [119], but its efficacy in human OA has not been clearly demonstrated [120]. Clinical trials of anti-TNF therapies are limited, and with mixed results [121–123]. Inhibiting the enzymes which directly cleave the cartilage matrix with MMP inhibitors have also been pursued as pharmacologic treatments. The use of MMP inhibitors in clinical trials, however, have resulted in severe musculoskeletal side effects including joint stiffness, inflammation, and pain, possibly due to their lack of specificity. MMPs are required for physiologic function in addition to the roles they play in OA [6,124]. Current efforts are now aimed at inhibition of specific MMPs, such as MMP-13 [125]. However, targeting only one molecule fails to address the broad and multimodal nature of OA, and may not effectively arrest or slow OA progression.

Recent studies suggest that ROS production induced by oxidative and other stresses may be a mediator of OA disease progression [126–128]. Elevated ROS production in conditions such as post-traumatic stress and aging may increase chondrocyte senescence and/or cell death [129,130]. Patients with knee OA exhibit higher levels of oxidative stress [131], and oxidative stress-induced damage [132]. Furthermore, levels of superoxide dismutase antioxidant enzymes are reduced in OA cartilage and joint fluid [133,134]. Boosting antioxidant defenses protects cartilage from traumatic impact-induced cartilage degradation and reduces OA severity in animal models of OA [135–137]. Upon further validation, these most recent progresses highly suggest that targeting altered response regulation against oxidative and other stresses should be a major criteria in developing effective nutraceutical-based products for OA prevention and treatment.

#### 4.2. Molecular Targeting of OA by Nutraceuticals

The molecular targets of OA can be categorized as inflammatory, oxidative stress, or catabolic. These targets provide a significant rational foundation for pursuing nutraceuticals with anti-inflammatory, anti-catabolic activity, and anti-stress (*i.e.*, oxidative stress) properties for anti-OA nutraceutical drug selection and formulation. Nutraceuticals that have the potential to spontaneously target these aspects of OA may be the most druggable for molecular targeting of OA.

While OA is a complex disease with an unclear etiology and multiple risk factors, recent studies suggest the following are critical for OA initiation and disease progression: over activated catabolic activity mediated primarily by pro-inflammatory cytokines (*i.e.*, IL-1, TNF- $\alpha$ ); deleterious stresses such as oxidative stress as well as the defense mechanisms against these stress factors (*i.e.*, oxidative stress); proteolytic enzymes which directly degrade the cartilage matrix such as matrix metalloproteinases, MMPs and aggrecanases, ADAMTS.

#### 4.3. Anti-Inflammatory

Pomegranate extracts exert anti-inflammatory actions by inhibiting the activity of NF- $\kappa$ B, COX-2 and PGE<sub>2</sub> [94,138]. Prodelphinidin—a condensed polymeric tannin that can be found in pomegranate—inhibited PGE<sub>2</sub> synthesis by down-regulating COX-2 in human chondrocytes [139]. Ginger extract has been demonstrated to decrease the IL-1 $\beta$  and LPS-induced production of NO and PGE<sub>2</sub> in OA cartilage [140]. Furthermore, ginger extract was effective in inhibiting the production of TNF- $\alpha$ , PGE<sub>2</sub>, and COX-2 expression in human synoviocytes by regulating NF- $\kappa$ B activation and degradation of its inhibitor I $\kappa$ B- $\alpha$  [141]. It has also been reported to decrease the IL-1 $\beta$ -induced expression of TNF- $\alpha$  and TNF- $\alpha$ -induced production of COX-2 in synoviocytes [142]. Resveratrol is a polyphenolic phytoalexin present in grapes, berries, and peanuts. Resveratrol suppresses NF- $\kappa$ B-dependent pro-inflammatory products, including PGE<sub>2</sub> and COX-2 [143,144]. Resveratrol has also been shown to inhibit IL-1 $\beta$ -induced apoptosis by inhibiting caspase-3 and downregulating the NF- $\kappa$ B pathway in chondrocytes [145]. Epigallocatechin 3-gallate (EGCG), a bioactive polyphenol found in green tea, inhibits the production of inflammatory mediators including PGE<sub>2</sub>, COX-2, and NF- $\kappa$ B [146]. By inhibiting the NF- $\kappa$ B pathway, EGCG suppressed IL6, IL-8, and TNF- $\alpha$  in IL-1 $\beta$  stimulated human OA chondrocytes [147]. Curcumin inhibited IL-1 $\beta$ -induced NF- $\kappa$ B activation and translocation, resulting in reduced expression of NF- $\kappa$ B downstream pro-inflammatory gene COX-2 [90]. Curcumin also prevented production of NO, PGE<sub>2</sub>, IL-6, and IL-8 stimulated by IL-1 $\beta$  [96]. Rosehip preparations have anti-inflammatory properties, and have been shown to inhibit expression of iNOS and IL-1 $\alpha$ , and IL-1 $\beta$ -induced IL-1 $\alpha$  and IL-8 in chondrocytes. The combination of glucosamine and chondroitin sulfate suppressed gene expression of COX-2 and NF- $\kappa$ B induced by IL-1 in cartilage explants, leading to reduced production of NO and PGE<sub>2</sub> [148]. One of the mechanisms through which glucosamine or chondroitin sulfate exerts anti-inflammation is by inhibiting the IL-1 $\beta$  induced NF- $\kappa$ B pathway, resulting in a reduction in the COX-2 synthesis [149].

#### 4.4. Anti-Oxidative Stress

Inflammatory cytokines (e.g., IL-1 $\beta$  and TNF- $\alpha$ ) are known to stimulate chondrocytes and synoviocytes to produce high levels of oxygen free radicals [150]. Reactive oxygen species (ROS), which regulate many signaling pathways and pro-inflammatory cytokine gene activation, are important mediators in the pathogenesis of OA [151]. EGCG has been demonstrated to protect chondrocytes and other cell types from oxidative stress and ROS-mediated cytotoxicity [151–153]. EGCG pre-treatment of cells prevented H<sub>2</sub>O<sub>2</sub>-induced activation of MAPKs, suggesting EGCG has the potential to inhibit oxidative stress-mediated activation of inflammatory signaling pathways [154,155]. EGCG also increases innate antioxidant defenses, including expressions of catalase, superoxide dismutase, and glutathione peroxidase [155]. In addition, there is evidence that other nutraceuticals, such as ginger, may exert anti-oxidant effects [156]. The phenolic constituent of ginger, [6]-gingerol, inhibited LPS-induced iNOS expression and production of NO and other reactive nitrogen species in macrophages [157]. One of the components derived from pomegranate, anthocyanin, is a potent antioxidant, and has been reported to decrease lipid peroxidation and enhance activities of antioxidants catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase in the liver [158,159].

#### 4.5. Anti-Catabolic/Proteolytic Enzymes

Cartilage degradation, mainly caused by overactive catabolic activity primarily due to MMPs and ADAMTS, has been recognized as a major target for OA prevention and treatment. EGCG has been shown to significantly inhibit the expression and activities of proteolytic enzymes, including MMP-1 and MMP-13, and ADAMTS-1, -4, and -5 in chondrocytes [160,161]. Catabolic activity in other joint tissues, including synoviocytes and tendon, can also be suppressed by EGCG. EGCG suppressed TNF- $\alpha$ -induced production of MMP-1 and MMP-3 in RA synoviocytes and IL-1 $\beta$ -induced MMP-1, -3 and -13 expressions in human tendon fibroblasts [162]. Studies have also documented that EGCG increases anti-catabolic activity by inducing expression and activity of tissue inhibitors of MMPs (TIMP)-1 and -2 *in vitro* [163,164]. Curcumin exhibits an anti-catabolic effect by inhibiting MMP-3 and MMP-9 [96,165]. Curcumin also suppressed the release of proteoglycans in equine cartilage explants stimulated with IL-1 $\beta$  [166]. In other joint tissues, curcumin inhibited the IL-1 $\beta$ -induced production of MMP-1, MMP-9, and MMP-13 in tenocytes [167].

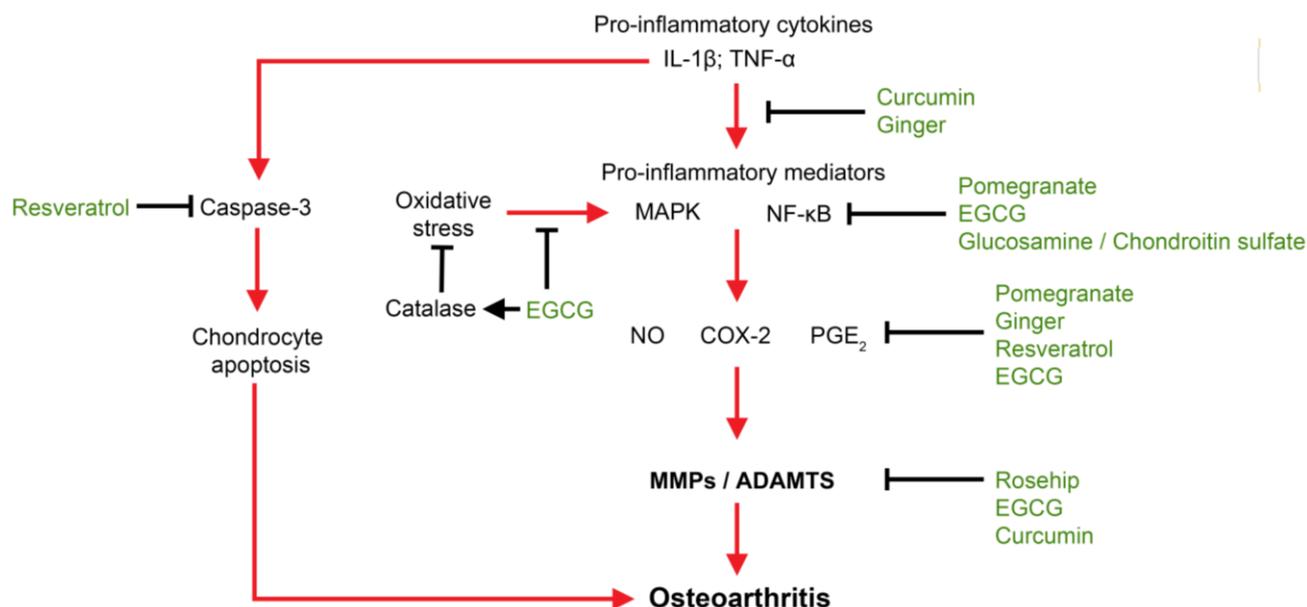
### 5. Conclusions

Nutraceuticals have been demonstrated to effectively suppress over activated inflammation and catabolic activity, and oxidative stress-induced deleterious responses. The suppression of inflammation and catabolic activity, in particular, are important properties of drugs targeting OA.

Current pre-clinical and clinical trial data are promising, and show that individual nutraceutical compounds exert beneficial effects on OA, such as relieving pain and improving function. Their effects on disease modification have not yet been clearly demonstrated, or are still under investigation. Based on the effectiveness and actions of these nutraceutical compounds, efficacy of using an individual compound to treat a complex and chronic disease with multiple risk factors such as OA, may be limited. Future nutraceutical-based approaches may require a combination of compounds, and

the selected compounds should: exert active effects on OA targets such as inflammation and catabolism, suppress oxidative stress and relieve chronic pain, as well as exerting complementary, additive, and/or synergistic anti-arthritic effects with other compounds within the formulation. These novel nutraceutical-based compound formulations which “shoot” many of the OA molecular targets (Figure 1) may serve as a therapeutic strategy for a new generation of nutraceuticals in OA prevention and treatment.

**Figure 1.** Molecular OA targeting of select nutraceuticals. Research findings support the concept that nutraceuticals can be used in a complementary manner to “shoot” multiple OA molecular targets.



## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Lawrence, R.C.; Felson, D.T.; Helmick, C.G.; Arnold, L.M.; Choi, H.; Deyo, R.A.; Gabriel, S.; Hirsch, R.; Hochberg, M.C.; Hunder, G.G.; *et al.* Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum* **2008**, *58*, 26–35.
2. Suri, P.; Morgenroth, D.C.; Hunter, D.J. Epidemiology of osteoarthritis and associated comorbidities. *PM R* **2012**, *4*, S10–S19.
3. Kotlarz, H.; Gunnarsson, C.L.; Fang, H.; Rizzo, J.A. Insurer and out-of-pocket costs of osteoarthritis in the US: Evidence from national survey data. *Arthritis Rheum* **2009**, *60*, 3546–3553.
4. Loeser, R.F.; Goldring, S.R.; Scanzello, C.R.; Goldring, M.B. Osteoarthritis: A disease of the joint as an organ. *Arthritis Rheum* **2012**, *64*, 1697–1707.
5. Burr, D.B.; Gallant, M.A. Bone remodelling in osteoarthritis. *Nat. Rev. Rheumatol.* **2012**, *8*, 665–673.

6. Le Graverand-Gastineau, M.P. Disease modifying osteoarthritis drugs: Facing development challenges and choosing molecular targets. *Curr. Drug Targets* **2010**, *11*, 528–535.
7. Evans, C.H.; Ghivizzani, S.C.; Robbins, P.D. Getting arthritis gene therapy into the clinic. *Nat. Rev. Rheumatol.* **2011**, *7*, 244–249.
8. Heinegard, D.; Saxne, T. The role of the cartilage matrix in osteoarthritis. *Nat. Rev. Rheumatol.* **2011**, *7*, 50–56.
9. Sun, H.B. Mechanical loading, cartilage degradation, and arthritis. *Ann. N. Y. Acad. Sci.* **2010**, *1211*, 37–50.
10. Hashimoto, M.; Nakasa, T.; Hikata, T.; Asahara, H. Molecular network of cartilage homeostasis and osteoarthritis. *Med. Res. Rev.* **2008**, *28*, 464–481.
11. Cheng, D.S.; Visco, C.J. Pharmaceutical therapy for osteoarthritis. *PM&R* **2012**, *4*, S82–S88.
12. Patrignani, P.; Tacconelli, S.; Bruno, A.; Sostres, C.; Lanas, A. Managing the adverse effects of nonsteroidal anti-inflammatory drugs. *Exp. Rev. Clin. Pharm.* **2011**, *4*, 605–621.
13. Henrotin, Y.; Lambert, C.; Couchourel, D.; Ripoll, C.; Chiotelli, E. Nutraceuticals: Do they represent a new era in the management of osteoarthritis?—A narrative review from the lessons taken with five products. *Osteoarthr. Cartilage* **2011**, *19*, 1–21.
14. Akhtar, N.; Haqqi, T.M. Current nutraceuticals in the management of osteoarthritis: A review. *Ther. Adv. Musculoskelet Dis.* **2012**, *4*, 181–207.
15. Shen, C.L.; Smith, B.J.; Lo, D.F.; Chyu, M.C.; Dunn, D.M.; Chen, C.H.; Kwun, I.S. Dietary polyphenols and mechanisms of osteoarthritis. *J. Nutr. Biochem.* **2012**, *23*, 1367–1377.
16. Guimaraes, A.G.; Xavier, M.A.; de Santana, M.T.; Camargo, E.A.; Santos, C.A.; Brito, F.A.; Barreto, E.O.; Cavalcanti, S.C.; Antonioli, A.R.; Oliveira, R.C.; *et al.* Carvacrol attenuates mechanical hypernociception and inflammatory response. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **2012**, *385*, 253–263.
17. Cavalcante Melo, F.H.; Rios, E.R.; Rocha, N.F.; Cito Mdo, C.; Fernandes, M.L.; De Sousa, D.P.; De Vasconcelos, S.M.; De Sousa, F.C. Antinociceptive activity of carvacrol (5-isopropyl-2-methylphenol) in mice. *J. Pharm. Pharmacol.* **2012**, *64*, 1722–1729.
18. Guimaraes, A.G.; Oliveira, G.F.; Melo, M.S.; Cavalcanti, S.C.; Antonioli, A.R.; Bonjardim, L.R.; Silva, F.A.; Santos, J.P.; Rocha, R.F.; *et al.* Bioassay-guided evaluation of antioxidant and antinociceptive activities of carvacrol. *Basic Clin. Pharmacol. Toxicol.* **2010**, *107*, 949–957.
19. Henrotin, Y.; Clutterbuck, A.L.; Allaway, D.; Lodwig, E.M.; Harris, P.; Mathy-Hartert, M.; Shakibaei, M.; Mobasheri, A. Biological actions of curcumin on articular chondrocytes. *Osteoarthr. Cartilage* **2010**, *18*, 141–149.
20. Sreejayan; Rao, M.N. Nitric oxide scavenging by curcuminoids. *J. Pharm. Pharmacol.* **1997**, *49*, 105–107.
21. Black, C.; Clar, C.; Henderson, R.; MacEachern, C.; McNamee, P.; Quayyum, Z.; Royle, P.; Thomas, S. The clinical effectiveness of glucosamine and chondroitin supplements in slowing or arresting progression of osteoarthritis of the knee: A systematic review and economic evaluation. *Health Tech. Assess.* **2009**, *13*, 1–148.
22. Roughley, P.J. The structure and function of cartilage proteoglycans. *Eur. Cell Mater.* **2006**, *12*, 92–101.

23. Clegg, D.O.; Reda, D.J.; Harris, C.L.; Klein, M.A.; O'Dell, J.R.; Hooper, M.M.; Bradley, J.D.; Bingham, C.O., 3rd; Weisman, M.H.; Jackson, C.G.; *et al.* Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N. Engl. J. Med.* **2006**, *354*, 795–808.
24. Sawitzke, A.D.; Shi, H.; Finco, M.F.; Dunlop, D.D.; Bingham, C.O., 3rd; Harris, C.L.; Singer, N.G.; Bradley, J.D.; Silver, D.; Jackson, C.G.; *et al.* The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: A report from the glucosamine/chondroitin arthritis intervention trial. *Arthritis Rheum.* **2008**, *58*, 3183–3191.
25. Sawitzke, A.D.; Shi, H.; Finco, M.F.; Dunlop, D.D.; Harris, C.L.; Singer, N.G.; Bradley, J.D.; Silver, D.; Jackson, C.G.; Lane, N.E.; *et al.* Clinical efficacy and safety of glucosamine, chondroitin sulphate, their combination, celecoxib or placebo taken to treat osteoarthritis of the knee: 2-year results from GAIT. *Ann. Rheum. Dis.* **2010**, *69*, 1459–1464.
26. Gupta, P.K.; Samarakoon, S.M.; Chandola, H.M.; Ravishankar, B. Clinical evaluation of *Boswellia serrata* (Shallaki) resin in the management of Sandhivata (osteoarthritis). *Ayu* **2011**, *32*, 478–482.
27. Krishnaraju, A.V.; Sundararaju, D.; Vamsikrishna, U.; Suryachandra, R.; Machiraju, G.; Sengupta, K.; Trimurtulu, G. Safety and toxicological evaluation of Aflapin: A novel *Boswellia*-derived anti-inflammatory product. *Toxicol. Mech. Method* **2010**, *20*, 556–563.
28. Kimmatkar, N.; Thawani, V.; Hingorani, L.; Khiyani, R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee—A randomized double blind placebo controlled trial. *Phytomedicine* **2003**, *10*, 3–7.
29. Sengupta, K.; Kolla, J.N.; Krishnaraju, A.V.; Yalamanchili, N.; Rao, C.V.; Golakoti, T.; Raychaudhuri, S.; Raychaudhuri, S.P. Cellular and molecular mechanisms of anti-inflammatory effect of Aflapin: A novel *Boswellia serrata* extract. *Mol. Cell Biochem.* **2011**, *354*, 189–197.
30. Brien, S.; Lewith, G.; Walker, A.F.; Middleton, R.; Prescott, P.; Bundy, R. Bromelain as an adjunctive treatment for moderate-to-severe osteoarthritis of the knee: A randomized placebo-controlled pilot study. *QJM* **2006**, *99*, 841–850.
31. Brien, S.; Lewith, G.; Walker, A.; Hicks, S.M.; Middleton, D. Bromelain as a treatment for osteoarthritis: A review of clinical studies. *Evid. based Compl. Alternative Med.* **2004**, *1*, 251–257.
32. Wu, S.Q.; Otero, M.; Unger, F.M.; Goldring, M.B.; Phrutivorapongkul, A.; Chiari, C.; Kolb, A.; Viernstein, H.; Toegel, S. Anti-inflammatory activity of an ethanolic *Caesalpinia sappan* extract in human chondrocytes and macrophages. *J. Ethnopharmacol.* **2011**, *138*, 364–372.
33. Toegel, S.; Wu, S.Q.; Otero, M.; Goldring, M.B.; Leelapornpisid, P.; Chiari, C.; Kolb, A.; Unger, F.M.; Windhager, R.; Viernstein, H. *Caesalpinia sappan* extract inhibits IL1beta-mediated overexpression of matrix metalloproteinases in human chondrocytes. *Genes Nutr.* **2012**, *7*, 307–318.
34. Kosuwon, W.; Sirichatiwapee, W.; Wisanuyotin, T.; Jeeravipoolvarn, P.; Laupattarakasem, W. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin *versus* placebo. *J. Med. Assoc. Thailand* **2010**, *93*, 1188–1195.
35. Remadevi, R.; Szallisi, A. Adlea (ALGRX-4975), an injectable capsaicin (TRPV1 receptor agonist) formulation for longlasting pain relief. *IDrugs* **2008**, *11*, 120–132.

36. McKay, L.; Gemmell, H.; Jacobson, B.; Hayes, B. Effect of a topical herbal cream on the pain and stiffness of osteoarthritis: A randomized double-blind, placebo-controlled clinical trial. *J. Clin. Rheumatol.* **2003**, *9*, 164–169.
37. Engler, A.; Aeschlimann, A.; Simmen, B.R.; Michel, B.A.; Gay, R.E.; Gay, S.; Sprott, H. Expression of transient receptor potential vanilloid 1 (TRPV1) in synovial fibroblasts from patients with osteoarthritis and rheumatoid arthritis. *Biochem. Biophys. Res. Commun.* **2007**, *359*, 884–888.
38. Piscocoya, J.; Rodriguez, Z.; Bustamante, S.A.; Okuhama, N.N.; Miller, M.J.; Sandoval, M. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: Mechanisms of action of the species *Uncaria guianensis*. *Inflamm. Res.* **2001**, *50*, 442–448.
39. Rosenbaum, C.C.; O'Mathuna, D.P.; Chavez, M.; Shields, K. Antioxidants and antiinflammatory dietary supplements for osteoarthritis and rheumatoid arthritis. *Altern. Ther. Health Med.* **2010**, *16*, 32–40.
40. Olsen, N.J.; Branch, V.K.; Jonnala, G.; Seskar, M.; Cooper, M. Phase 1, placebo-controlled, dose escalation trial of chicory root extract in patients with osteoarthritis of the hip or knee. *BMC Musculoskelet. Disord.* **2010**, *11*, 156.
41. Cavin, C.; Delannoy, M.; Malnoe, A.; Debeffe, E.; Touche, A.; Courtois, D.; Schilter, B. Inhibition of the expression and activity of cyclooxygenase-2 by chicory extract. *Biochem. Biophys. Res. Commun.* **2005**, *327*, 742–749.
42. Schmidt, B.M.; Ilic, N.; Poulev, A.; Raskin, I. Toxicological evaluation of a chicory root extract. *Food Chem. Toxicol.* **2007**, *45*, 1131–1139.
43. Chen, W.P.; Tang, J.L.; Bao, J.P.; Hu, P.F.; Yu, C.; Shi, Z.L.; Wu, L.D. Effects of diallyl sulphide in chondrocyte and cartilage in experimental osteoarthritis in rabbit. *Phytother. Res.* **2011**, *25*, 351–356.
44. Lee, H.S.; Lee, C.H.; Tsai, H.C.; Salter, D.M. Inhibition of cyclooxygenase 2 expression by diallyl sulfide on joint inflammation induced by urate crystal and IL-1beta. *Osteoarthr. Cartilage* **2009**, *17*, 91–99.
45. Lai, J.N.; Chen, H.J.; Chen, C.C.; Lin, J.H.; Hwang, J.S.; Wang, J.D. Duhuo jisheng tang for treating osteoarthritis of the knee: A prospective clinical observation. *Chinese Med.* **2007**, *2*, 4.
46. Chantre, P.; Cappelaere, A.; Leblan, D.; Guedon, D.; Vandermander, J.; Fournie, B. Efficacy and tolerance of *Harpagophytum procumbens* versus diacerhein in treatment of osteoarthritis. *Phytomedicine* **2000**, *7*, 177–183.
47. Chrubasik, S.; Thanner, J.; Kunzel, O.; Conradt, C.; Black, A.; Pollak, S. Comparison of outcome measures during treatment with the proprietary *Harpagophytum* extract doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* **2002**, *9*, 181–194.
48. Chrubasik, J.E.; Roufogalis, B.D.; Chrubasik, S. Evidence of effectiveness of herbal antiinflammatory drugs in the treatment of painful osteoarthritis and chronic low back pain. *Phytother. Res.* **2007**, *21*, 675–683.
49. Fiebich, B.L.; Munoz, E.; Rose, T.; Weiss, G.; McGregor, G.P. Molecular targets of the antiinflammatory *Harpagophytum procumbens* (devil's claw): Inhibition of *TNFalpha* and *COX-2* gene expression by preventing activation of AP-1. *Phytother. Res.* **2012**, *26*, 806–811.

50. Sumantran, V.N.; Kulkarni, A.; Chandwaskar, R.; Harsulkar, A.; Patwardhan, B.; Chopra, A.; Wagh, U.V. Chondroprotective potential of fruit extracts of *Phyllanthus emblica* in Osteoarthritis. *Evid. Base. Compl. Alternative Med.* **2008**, *5*, 329–335.
51. Uehleke, B.; Muller, J.; Stange, R.; Kelber, O.; Melzer, J. Willow bark extract STW 33-I in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain. *Phytotherapy* **2013**, *20*, 980–984.
52. Schmid, B.; Ludtke, R.; Selbmann, H.K.; Kotter, I.; Tschirdewahn, B.; Schaffner, W.; Heide, L. Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: Randomized placebo-controlled, double blind clinical trial. *Phytother. Res.* **2001**, *15*, 344–350.
53. Cowan, D. Oral Aloe vera as a treatment for osteoarthritis: A summary. *Brit. J. Comm. Nur.* **2010**, *15*, 280–282.
54. Christensen, R.; Bartels, E.M.; Astrup, A.; Bliddal, H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: A meta-analysis of randomized controlled trials. *Osteoarthr. Cartilage* **2008**, *16*, 399–408.
55. Appelboom, T.; Schuermans, J.; Verbruggen, G.; Henrotin, Y.; Reginster, J.Y. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study. *Scand. J. Rheumatol.* **2001**, *30*, 242–247.
56. Boileau, C.; Martel-Pelletier, J.; Caron, J.; Msika, P.; Guillou, G.B.; Baudouin, C.; Pelletier, J.P. Protective effects of total fraction of avocado/soybean unsaponifiables on the structural changes in experimental dog osteoarthritis: Inhibition of nitric oxide synthase and matrix metalloproteinase-13. *Arthritis Res. Ther.* **2009**, *11*, R41.
57. Au, R.Y.; Al-Talib, T.K.; Au, A.Y.; Phan, P.V.; Frondoza, C.G. Avocado soybean unsaponifiables (ASU) suppress *TNF-alpha*, *IL-1beta*, *COX-2*, *iNOS* gene expression, and prostaglandin E2 and nitric oxide production in articular chondrocytes and monocyte/macrophages. *Osteoarthr. Cartilage* **2007**, *15*, 1249–1255.
58. Scorei, R.I.; Rotaru, P. Calcium fructoborate—Potential anti-inflammatory agent. *Biol. Trace Element Res.* **2011**, *143*, 1223–1238.
59. Bello, A.E.; Oesser, S. Collagen hydrolysate for the treatment of osteoarthritis and other joint disorders: A review of the literature. *Curr. Med. Res. Opin.* **2006**, *22*, 2221–2232.
60. Van Vlijven, J.P.; Luijsterburg, P.A.; Verhagen, A.P.; van Osch, G.J.; Kloppenburg, M.; Bierma-Zeinstra, S.M. Symptomatic and chondroprotective treatment with collagen derivatives in osteoarthritis: A systematic review. *Osteoarthr. Cartilage* **2012**, *20*, 809–821.
61. Chua, K.H.; Lee, T.H.; Nagandran, K.; Md Yahaya, N.H.; Lee, C.T.; Tjih, E.T.; Abdul Aziz, R. Edible Bird's nest extract as a chondro-protective agent for human chondrocytes isolated from osteoarthritic knee: *In vitro* study. *BMC Compl. Alternative Med.* **2013**, *13*, 19.
62. Hooshmand, S.; Soung do, Y.; Lucas, E.A.; Madihally, S.V.; Levenson, C.W.; Arjmandi, B.H. Genistein reduces the production of proinflammatory molecules in human chondrocytes. *J. Nutr. Biochem.* **2007**, *18*, 609–614.
63. Coulson, S.; Vecchio, P.; Gramotnev, H.; Vitetta, L. Green-lipped mussel (*Perna canaliculus*) extract efficacy in knee osteoarthritis and improvement in gastrointestinal dysfunction: A pilot study. *Inflammopharmacology* **2012**, *20*, 71–76.

64. Halpern, G.M. Anti-inflammatory effects of a stabilized lipid extract of *Perna canaliculus* (Lyprinol). *Allerg. Immunol.* **2000**, *32*, 272–278.
65. So, J.S.; Song, M.K.; Kwon, H.K.; Lee, C.G.; Chae, C.S.; Sahoo, A.; Jash, A.; Lee, S.H.; Park, Z.Y.; Im, S.H. *Lactobacillus casei* enhances type II collagen/glucosamine-mediated suppression of inflammatory responses in experimental osteoarthritis. *Life Sci.* **2011**, *88*, 358–366.
66. Kim, L.S.; Axelrod, L.J.; Howard, P.; Buratovich, N.; Waters, R.F. Efficacy of methylsulfonylmethane (MSM) in osteoarthritis pain of the knee: A pilot clinical trial. *Osteoarthr. Cartilage* **2006**, *14*, 286–294.
67. Fox, R.B.; Fox, W.K. Dimethyl sulfoxide prevents hydroxyl radical-mediated depolymerization of hyaluronic acid. *Ann. N. Y. Acad. Sci.* **1983**, *411*, 14–18.
68. Parcell, S. Sulfur in human nutrition and applications in medicine. *Altern. Med. Rev.* **2002**, *7*, 22–44.
69. Baker, K.R.; Matthan, N.R.; Lichtenstein, A.H.; Niu, J.; Guermazi, A.; Roemer, F.; Grainger, A.; Nevitt, M.C.; Clancy, M.; Lewis, C.E.; *et al.* Association of plasma *n*-6 and *n*-3 polyunsaturated fatty acids with synovitis in the knee: The MOST study. *Osteoarthr. Cartilage* **2012**, *20*, 382–387.
70. Curtis, C.L.; Rees, S.G.; Little, C.B.; Flannery, C.R.; Hughes, C.E.; Wilson, C.; Dent, C.M.; Otterness, I.G.; Harwood, J.L.; Caterson, B. Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to *n*-3 fatty acids. *Arthritis Rheum.* **2002**, *46*, 1544–1553.
71. Knott, L.; Avery, N.C.; Hollander, A.P.; Tarlton, J.F. Regulation of osteoarthritis by omega-3 (*n*-3) polyunsaturated fatty acids in a naturally occurring model of disease. *Osteoarthr. Cartilage* **2011**, *19*, 1150–1157.
72. Kim, J.; Lee, E.Y.; Koh, E.M.; Cha, H.S.; Yoo, B.; Lee, C.K.; Lee, Y.J.; Ryu, H.; Lee, K.H.; Song, Y.W. Comparative clinical trial of *S*-adenosylmethionine versus nabumetone for the treatment of knee osteoarthritis: An 8-week, multicenter, randomized, double-blind, double-dummy, Phase IV study in Korean patients. *Clin. Ther* **2009**, *31*, 2860–2872.
73. Najm, W.I.; Reinsch, S.; Hoehler, F.; Tobis, J.S.; Harvey, P.W. *S*-adenosyl methionine (SAME) versus celecoxib for the treatment of osteoarthritis symptoms: A double-blind cross-over trial. [ISRCTN36233495]. *BMC Musculoskelet Disord.* **2004**, *5*, 6.
74. Bradley, J.D.; Flusser, D.; Katz, B.P.; Schumacher, H.R., Jr.; Brandt, K.D.; Chambers, M.A.; Zonay, L.J. A randomized, double blind, placebo controlled trial of intravenous loading with *S*-adenosylmethionine (SAM) followed by oral SAM therapy in patients with knee osteoarthritis. *J. Rheumatol.* **1994**, *21*, 905–911.
75. Harmand, M.F.; Vilamitjana, J.; Maloche, E.; Duphil, R.; Ducassou, D. Effects of *S*-adenosylmethionine on human articular chondrocyte differentiation. An *in vitro* study. *Am. J. Med.* **1987**, *83*, 48–54.
76. Barcelo, H.A.; Wiemeyer, J.C.; Sagasta, C.L.; Macias, M.; Barreira, J.C. Effect of *S*-adenosylmethionine on experimental osteoarthritis in rabbits. *Am. J. Med.* **1987**, *83*, 55–59.
77. Jonas, W.B.; Rapoza, C.P.; Blair, W.F. The effect of niacinamide on osteoarthritis: A pilot study. *Inflamm. Res.* **1996**, *45*, 330–334.

78. Clark, A.G.; Rohrbaugh, A.L.; Otterness, I.; Kraus, V.B. The effects of ascorbic acid on cartilage metabolism in guinea pig articular cartilage explants. *Matrix Biol.* **2002**, *21*, 175–184.
79. McAlindon, T.; LaValley, M.; Schneider, E.; Nuite, M.; Lee, J.Y.; Price, L.L.; Lo, G.; Dawson-Hughes, B. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: A randomized controlled trial. *JAMA* **2013**, *309*, 155–162.
80. Sanghi, D.; Mishra, A.; Sharma, A.C.; Singh, A.; Natu, S.M.; Agarwal, S.; Srivastava, R.N. Does vitamin D improve osteoarthritis of the knee: A randomized controlled pilot trial. *Clin. Orthop. Relat. Res.* **2013**, *471*, 3556–3562.
81. Blankenhorn, G. Clinical effectiveness of Spondyvit (vitamin E) in activated arthroses. A multicenter placebo-controlled double-blind study. *Zeitschrift fur Orthopadie und ihre Grenzgebiete* **1986**, *124*, 340–343.
82. Brand, C.; Snaddon, J.; Bailey, M.; Cicuttini, F. Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: A six month double blind, randomised, placebo controlled study. *Ann. Rheum. Dis.* **2001**, *60*, 946–949.
83. Dixon, R.A.; Xie, D.Y.; Sharma, S.B. Proanthocyanidins—A final frontier in flavonoid research? *New Phytol.* **2005**, *165*, 9–28.
84. Miyake, M.; Ide, K.; Sasaki, K.; Matsukura, Y.; Shijima, K.; Fujiwara, D. Oral administration of highly oligomeric procyanidins of *Jatoba* reduces the severity of collagen-induced arthritis. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 1781–1788.
85. Hadipour-Jahromy, M.; Mozaffari-Kermani, R. Chondroprotective effects of pomegranate juice on monoiodoacetate-induced osteoarthritis of the knee joint of mice. *Phytother. Res.* **2010**, *24*, 182–185.
86. Bliddal, H.; Rosetzky, A.; Schlichting, P.; Weidner, M.S.; Andersen, L.A.; Ibfelt, H.H.; Christensen, K.; Jensen, O.N.; Barslev, J. A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. *Osteoarthr. Cartilage* **2000**, *8*, 9–12.
87. Altman, R.D.; Marcussen, K.C. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum.* **2001**, *44*, 2531–2538.
88. Kulkarni, R.R.; Patki, P.S.; Jog, V.P.; Gandage, S.G.; Patwardhan, B. Treatment of osteoarthritis with a herbomineral formulation: A double-blind, placebo-controlled, cross-over study. *J. Ethnopharmacol.* **1991**, *33*, 91–95.
89. Christensen, R.; Bartels, E.M.; Altman, R.D.; Astrup, A.; Bliddal, H. Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients? —A meta-analysis of randomized controlled trials. *Osteoarthr. Cartilage* **2008**, *16*, 965–972.
90. Csaki, C.; Mobasheri, A.; Shakibaei, M. Synergistic chondroprotective effects of curcumin and resveratrol in human articular chondrocytes: Inhibition of IL-1beta-induced NF-kappaB-mediated inflammation and apoptosis. *Arthritis Res. Ther.* **2009**, *11*, R165.
91. Doss, M.X.; Potta, S.P.; Hescheler, J.; Sachinidis, A. Trapping of growth factors by catechins: A possible therapeutic target for prevention of proliferative diseases. *J. Nutr. Biochem.* **2005**, *16*, 259–266.

92. Marotte, H.; Ruth, J.H.; Campbell, P.L.; Koch, A.E.; Ahmed, S. Green tea extract inhibits chemokine production, but up-regulates chemokine receptor expression, in rheumatoid arthritis synovial fibroblasts and rat adjuvant-induced arthritis. *Rheumatology* **2010**, *49*, 467–479.
93. Seeram, N.P.; Adams, L.S.; Henning, S.M.; Niu, Y.; Zhang, Y.; Nair, M.G.; Heber, D. *In vitro* antiproliferative, apoptotic and antioxidant activities of punicalagin, ellagic acid and a total pomegranate tannin extract are enhanced in combination with other polyphenols as found in pomegranate juice. *J. Nutr. Biochem.* **2005**, *16*, 360–367.
94. Ahmed, S.; Wang, N.; Hafeez, B.B.; Cheruvu, V.K.; Haqqi, T.M. *Punica granatum* L. extract inhibits IL-1beta-induced expression of matrix metalloproteinases by inhibiting the activation of MAP kinases and NF-kappaB in human chondrocytes *in vitro*. *J. Nutr.* **2005**, *135*, 2096–2102.
95. White, B. Ginger: An overview. *Am. Fam. Physician* **2007**, *75*, 1689–1691.
96. Mathy-Hartert, M.; Jacquemond-Collet, I.; Priem, F.; Sanchez, C.; Lambert, C.; Henrotin, Y. Curcumin inhibits pro-inflammatory mediators and metalloproteinase-3 production by chondrocytes. *Inflamm. Res.* **2009**, *58*, 899–908.
97. Ameye, L.G.; Chee, W.S. Osteoarthritis and nutrition. From nutraceuticals to functional foods: A systematic review of the scientific evidence. *Arthritis Res. Ther.* **2006**, *8*, R127.
98. Aggarwal, B.B.; Shishodia, S. Suppression of the nuclear factor-kappaB activation pathway by spice-derived phytochemicals: Reasoning for seasoning. *Ann. N. Y. Acad. Sci.* **2004**, *1030*, 434–441.
99. Mobasheri, A. Intersection of inflammation and herbal medicine in the treatment of osteoarthritis. *Curr. Rheumatol. Rep.* **2012**, *14*, 604–616.
100. Goldring, M.B.; Marcu, K.B. Cartilage homeostasis in health and rheumatic diseases. *Arthritis Res. Ther.* **2009**, *11*, 224.
101. Aigner, T.; Soder, S.; Gebhard, P.M.; McAlinden, A.; Haag, J. Mechanisms of disease: Role of chondrocytes in the pathogenesis of osteoarthritis—Structure, chaos and senescence. *Nat. Clin. Pract. Rheumatol.* **2007**, *3*, 391–399.
102. Pelletier, J.P.; Martel-Pelletier, J.; Abramson, S.B. Osteoarthritis, an inflammatory disease: Potential implication for the selection of new therapeutic targets. *Arthritis Rheum.* **2001**, *44*, 1237–1247.
103. Benito, M.J.; Veale, D.J.; FitzGerald, O.; van den Berg, W.B.; Bresnihan, B. Synovial tissue inflammation in early and late osteoarthritis. *Ann. Rheum. Dis.* **2005**, *64*, 1263–1267.
104. Kapoor, M.; Martel-Pelletier, J.; Lajeunesse, D.; Pelletier, J.P.; Fahmi, H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat. Rev. Rheumatol.* **2011**, *7*, 33–42.
105. Jerosch, J. Effects of glucosamine and chondroitin sulfate on cartilage metabolism in OA: Outlook on other nutrient partners especially omega-3 fatty acids. *Inter. J. Rheumatol.* **2011**, *2011*, 969012.
106. Milentijevic, D.; Rubel, I.F.; Liew, A.S.; Helfet, D.L.; Torzilli, P.A. An *in vivo* rabbit model for cartilage trauma: A preliminary study of the influence of impact stress magnitude on chondrocyte death and matrix damage. *J. Orthop. Trauma.* **2005**, *19*, 466–473.
107. Fernandes, J.C.; Martel-Pelletier, J.; Pelletier, J.P. The role of cytokines in osteoarthritis pathophysiology. *Biorheology* **2002**, *39*, 237–246.

108. Roman-Blas, J.A.; Jimenez, S.A. NF-kappaB as a potential therapeutic target in osteoarthritis and rheumatoid arthritis. *Osteoarthr. Cartilage* **2006**, *14*, 839–848.
109. Saklatvala, J. Inflammatory signaling in cartilage: MAPK and NF-kappaB pathways in chondrocytes and the use of inhibitors for research into pathogenesis and therapy of osteoarthritis. *Curr. Drug Targets* **2007**, *8*, 305–313.
110. Blom, A.B.; Brockbank, S.M.; van Lent, P.L.; van Beuningen, H.M.; Geurts, J.; Takahashi, N.; van der Kraan, P.M.; van de Loo, F.A.; Schreurs, B.W.; Clements, K.; *et al.* Involvement of the Wnt signaling pathway in experimental and human osteoarthritis: Prominent role of Wnt-induced signaling protein 1. *Arthritis Rheum.* **2009**, *60*, 501–512.
111. Chadjichristos, C.; Ghayor, C.; Kypriotou, M.; Martin, G.; Renard, E.; Ala-Kokko, L.; Suske, G.; de Crombrughe, B.; Pujol, J.P.; Galera, P. Sp1 and Sp3 transcription factors mediate interleukin-1 beta down-regulation of human type II collagen gene expression in articular chondrocytes. *J. Biol. Chem.* **2003**, *278*, 39762–39772.
112. Goldring, M.B.; Fukuo, K.; Birkhead, J.R.; Dudek, E.; Sandell, L.J. Transcriptional suppression by interleukin-1 and interferon-gamma of type II collagen gene expression in human chondrocytes. *J. Cell Biochem.* **1994**, *54*, 85–99.
113. Seguin, C.A.; Bernier, S.M. TNFalpha suppresses link protein and type II collagen expression in chondrocytes: Role of MEK1/2 and NF-kappaB signaling pathways. *J. Cell Physiol.* **2003**, *197*, 356–369.
114. Saklatvala, J. Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature* **1986**, *322*, 547–549.
115. Mengshol, J.A.; Vincenti, M.P.; Coon, C.I.; Barchowsky, A.; Brinckerhoff, C.E. Interleukin-1 induction of collagenase 3 (matrix metalloproteinase 13) gene expression in chondrocytes requires p38, c-Jun N-terminal kinase, and nuclear factor kappaB: Differential regulation of collagenase 1 and collagenase 3. *Arthritis Rheum.* **2000**, *43*, 801–811.
116. Lefebvre, V.; Peeters-Joris, C.; Vaes, G. Modulation by interleukin 1 and tumor necrosis factor alpha of production of collagenase, tissue inhibitor of metalloproteinases and collagen types in differentiated and dedifferentiated articular chondrocytes. *Biochim. Biophys. Acta* **1990**, *1052*, 366–378.
117. Tortorella, M.D.; Malfait, A.M.; Deccico, C.; Arner, E. The role of ADAM-TS4 (aggrecanase-1) and ADAM-TS5 (aggrecanase-2) in a model of cartilage degradation. *Osteoarthr. Cartilage* **2001**, *9*, 539–552.
118. Abramson, S.B. Nitric oxide in inflammation and pain associated with osteoarthritis. *Arthritis Res. Ther.* **2008**, *10*, S2.
119. Caron, J.P.; Fernandes, J.C.; Martel-Pelletier, J.; Tardif, G.; Mineau, F.; Geng, C.; Pelletier, J.P. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. *Arthritis Rheum.* **1996**, *39*, 1535–1544.
120. Chevalier, X.; Goupille, P.; Beaulieu, A.D.; Burch, F.X.; Bensen, W.G.; Conrozier, T.; Loeuille, D.; Kivitz, A.J.; Silver, D.; Appleton, B.E. Intraarticular injection of anakinra in osteoarthritis of the knee: A multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Rheum.* **2009**, *61*, 344–352.

121. Grunke, M.; Schulze-Koops, H. Successful treatment of inflammatory knee osteoarthritis with tumour necrosis factor blockade. *Ann. Rheum. Dis.* **2006**, *65*, 555–556.
122. Fioravanti, A.; Fabbroni, M.; Cerase, A.; Galeazzi, M. Treatment of erosive osteoarthritis of the hands by intra-articular infliximab injections: A pilot study. *Rheumatol. Int.* **2009**, *29*, 961–965.
123. Magnano, M.D.; Chakravarty, E.F.; Broudy, C.; Chung, L.; Kelman, A.; Hillygus, J.; Genovese, M.C. A pilot study of tumor necrosis factor inhibition in erosive/inflammatory osteoarthritis of the hands. *J. Rheumatol.* **2007**, *34*, 1323–1327.
124. Renkiewicz, R.; Qiu, L.; Lesch, C.; Sun, X.; Devalaraja, R.; Cody, T.; Kaldjian, E.; Welgus, H.; Baragi, V. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. *Arthritis Rheum.* **2003**, *48*, 1742–1749.
125. Hellio Le Graverand-Gastineau, M.P. OA clinical trials: Current targets and trials for OA. Choosing molecular targets: What have we learned and where we are headed? *Osteoarthr. Cartilage* **2009**, *17*, 1393–1401.
126. Loeser, R.F. The effects of aging on the development of osteoarthritis. *HSS J.* **2012**, *8*, 18–19.
127. Loeser, R.F. Aging processes and the development of osteoarthritis. *Curr. Opin. Rheumatol.* **2013**, *25*, 108–113.
128. Zhuo, Q.; Yang, W.; Chen, J.; Wang, Y. Metabolic syndrome meets osteoarthritis. *Nat. Rev. Rheumatol.* **2012**, *8*, 729–737.
129. Aigner, T.; Richter, W. OA in 2011: Age-related OA—A concept emerging from infancy? *Nat. Rev. Rheumatol.* **2012**, *8*, 70–72.
130. Martin, J.A.; Buckwalter, J.A. Post-traumatic osteoarthritis: The role of stress induced chondrocyte damage. *Biorheology* **2006**, *43*, 517–521.
131. Kotani, K.; Sakane, N.; Kamimoto, M.; Taniguchi, N. Levels of reactive oxygen metabolites in patients with knee osteoarthritis. *Australas J. Ageing* **2011**, *30*, 231–233.
132. Loeser, R.F.; Carlson, C.S.; Del Carlo, M.; Cole, A. Detection of nitrotyrosine in aging and osteoarthritic cartilage: Correlation of oxidative damage with the presence of interleukin-1beta and with chondrocyte resistance to insulin-like growth factor 1. *Arthritis Rheum.* **2002**, *46*, 2349–2357.
133. Scott, J.L.; Gabrielides, C.; Davidson, R.K.; Swingler, T.E.; Clark, I.M.; Wallis, G.A.; Boot-Handford, R.P.; Kirkwood, T.B.; Taylor, R.W.; Young, D.A. Superoxide dismutase downregulation in osteoarthritis progression and end-stage disease. *Ann. Rheum. Dis.* **2010**, *69*, 1502–1510.
134. Regan, E.A.; Bowler, R.P.; Crapo, J.D. Joint fluid antioxidants are decreased in osteoarthritic joints compared to joints with macroscopically intact cartilage and subacute injury. *Osteoarthr. Cartilage* **2008**, *16*, 515–521.
135. Moon, S.J.; Woo, Y.J.; Jeong, J.H.; Park, M.K.; Oh, H.J.; Park, J.S.; Kim, E.K.; Cho, M.L.; Park, S.H.; Kim, H.Y.; *et al.* Rebamipide attenuates pain severity and cartilage degeneration in a rat model of osteoarthritis by downregulating oxidative damage and catabolic activity in chondrocytes. *Osteoarthr. Cartilage* **2012**, *20*, 1426–1438.
136. Ramakrishnan, P.; Hecht, B.A.; Pedersen, D.R.; Lavery, M.R.; Maynard, J.; Buckwalter, J.A.; Martin, J.A. Oxidant conditioning protects cartilage from mechanically induced damage. *J. Orthop. Res.* **2010**, *28*, 914–920.

137. Woo, Y.J.; Joo, Y.B.; Jung, Y.O.; Ju, J.H.; Cho, M.L.; Oh, H.J.; Jhun, J.Y.; Park, M.K.; Park, J.S.; Kang, C.M.; *et al.* Grape seed proanthocyanidin extract ameliorates monosodium iodoacetate-induced osteoarthritis. *Exp. Mol. Med.* **2011**, *43*, 561–570.
138. Rasheed, Z.; Akhtar, N.; Haqqi, T.M. Pomegranate extract inhibits the interleukin-1beta-induced activation of MKK-3, p38alpha-MAPK and transcription factor RUNX-2 in human osteoarthritis chondrocytes. *Arthritis Res. Ther.* **2010**, *12*, R195.
139. Garbacki, N.; Angenot, L.; Bassleer, C.; Damas, J.; Tits, M. Effects of prodelfinidins isolated from *Ribes nigrum* on chondrocyte metabolism and COX activity. *Naunyn. Schmiedeberg's Arch. Pharmacol.* **2002**, *365*, 434–441.
140. Shen, C.L.; Hong, K.J.; Kim, S.W. Effects of ginger (*Zingiber officinale* Rosc.) on decreasing the production of inflammatory mediators in sow osteoarthrotic cartilage explants. *J. Med. Food* **2003**, *6*, 323–328.
141. Thomson, M.; Al-Qattan, K.K.; Al-Sawan, S.M.; Alnaqeeb, M.A.; Khan, I.; Ali, M. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. *Prostag. Leukotr. Ess.* **2002**, *67*, 475–478.
142. Frondoza, C.G.; Sohrabi, A.; Polotsky, A.; Phan, P.V.; Hungerford, D.S.; Lindmark, L. An *in vitro* screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. *In Vitro Cell Dev. Biol. Anim.* **2004**, *40*, 95–101.
143. Shakibaei, M.; Csaki, C.; Nebrich, S.; Mobasheri, A. Resveratrol suppresses interleukin-1beta-induced inflammatory signaling and apoptosis in human articular chondrocytes: Potential for use as a novel nutraceutical for the treatment of osteoarthritis. *Biochem. Pharmacol.* **2008**, *76*, 1426–1439.
144. Csaki, C.; Keshishzadeh, N.; Fischer, K.; Shakibaei, M. Regulation of inflammation signalling by resveratrol in human chondrocytes *in vitro*. *Biochem. Pharmacol.* **2008**, *75*, 677–687.
145. Shakibaei, M.; John, T.; Seifarth, C.; Mobasheri, A. Resveratrol inhibits IL-1 beta-induced stimulation of caspase-3 and cleavage of PARP in human articular chondrocytes *in vitro*. *Ann. N. Y. Acad. Sci.* **2007**, *1095*, 554–563.
146. Schulze-Tanzil, G.; Mobasheri, A.; Sendzik, J.; John, T.; Shakibaei, M. Effects of curcumin (diferuloylmethane) on nuclear factor kappaB signaling in interleukin-1beta-stimulated chondrocytes. *Ann. N. Y. Acad. Sci.* **2004**, *1030*, 578–586.
147. Sreejayan, N.; Rao, M.N. Free radical scavenging activity of curcuminoids. *Arzneimittelforschung* **1996**, *46*, 169–171.
148. Chan, P.S.; Caron, J.P.; Orth, M.W. Short-term gene expression changes in cartilage explants stimulated with interleukin beta plus glucosamine and chondroitin sulfate. *J. Rheumatol.* **2006**, *33*, 1329–1340.
149. Largo, R.; Alvarez-Soria, M.A.; Diez-Ortego, I.; Calvo, E.; Sanchez-Pernaute, O.; Egido, J.; Herrero-Beaumont, G. Glucosamine inhibits IL-1beta-induced NFkappaB activation in human osteoarthritic chondrocytes. *Osteoarthr. Cartilage* **2003**, *11*, 290–298.
150. Henrotin, Y.; Deby-Dupont, G.; Deby, C.; De Bruyn, M.; Lamy, M.; Franchimont, P. Production of active oxygen species by isolated human chondrocytes. *Br. J. Rheumatol.* **1993**, *32*, 562–567.

151. Lo, Y.Y.; Wong, J.M.; Cruz, T.F. Reactive oxygen species mediate cytokine activation of c-Jun NH<sub>2</sub>-terminal kinases. *J. Biol. Chem.* **1996**, *271*, 15703–15707.
152. Song, D.U.; Jung, Y.D.; Chay, K.O.; Chung, M.A.; Lee, K.H.; Yang, S.Y.; Shin, B.A.; Ahn, B.W. Effect of drinking green tea on age-associated accumulation of Maillard-type fluorescence and carbonyl groups in rat aortic and skin collagen. *Arch. Biochem. Biophys.* **2002**, *397*, 424–429.
153. Bordoni, A.; Hrelia, S.; Angeloni, C.; Giordano, E.; Guarnieri, C.; Caldarera, C.M.; Biagi, P.L. Green tea protection of hypoxia/reoxygenation injury in cultured cardiac cells. *J. Nutr. Biochem.* **2002**, *13*, 103–111.
154. Katiyar, S.K.; Afaq, F.; Azizuddin, K.; Mukhtar, H. Inhibition of UVB-induced oxidative stress-mediated phosphorylation of mitogen-activated protein kinase signaling pathways in cultured human epidermal keratinocytes by green tea polyphenol (–)-epigallocatechin-3-gallate. *Toxicol. Appl. Pharmacol.* **2001**, *176*, 110–117.
155. Meng, Q.; Velalar, C.N.; Ruan, R. Effects of epigallocatechin-3-gallate on mitochondrial integrity and antioxidative enzyme activity in the aging process of human fibroblast. *Free Radic. Biol. Med.* **2008**, *44*, 1032–1041.
156. Ippoushi, K.; Azuma, K.; Ito, H.; Horie, H.; Higashio, H. [6]-Gingerol inhibits nitric oxide synthesis in activated J774.1 mouse macrophages and prevents peroxynitrite-induced oxidation and nitration reactions. *Life Sci.* **2003**, *73*, 3427–3437.
157. Pan, M.H.; Hsieh, M.C.; Hsu, P.C.; Ho, S.Y.; Lai, C.S.; Wu, H.; Sang, S.; Ho, C.T. 6-Shogaol suppressed lipopolysaccharide-induced up-expression of iNOS and COX-2 in murine macrophages. *Mol. Nutr. Food Res.* **2008**, *52*, 1467–1477.
158. Seeram, N.P.; Nair, M.G. Inhibition of lipid peroxidation and structure-activity-related studies of the dietary constituents anthocyanins, anthocyanidins, and catechins. *J. Agric. Food Chem.* **2002**, *50*, 5308–5312.
159. Sudheesh, S.; Vijayalakshmi, N.R. Flavonoids from *Punica granatum*—Potential antiperoxidative agents. *Fitoterapia* **2005**, *76*, 181–186.
160. Ahmed, S.; Wang, N.; Lalonde, M.; Goldberg, V.M.; Haqqi, T.M. Green tea polyphenol epigallocatechin-3-gallate (EGCG) differentially inhibits interleukin-1 beta-induced expression of matrix metalloproteinase-1 and -13 in human chondrocytes. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 767–773.
161. Vankemmelbeke, M.N.; Jones, G.C.; Fowles, C.; Ilic, M.Z.; Handley, C.J.; Day, A.J.; Knight, C.G.; Mort, J.S.; Buttle, D.J. Selective inhibition of ADAMTS-1, -4 and -5 by catechin gallate esters. *Eur. J. Biochem.* **2003**, *270*, 2394–2403.
162. Yun, H.J.; Yoo, W.H.; Han, M.K.; Lee, Y.R.; Kim, J.S.; Lee, S.I. Epigallocatechin-3-gallate suppresses TNF-alpha-induced production of MMP-1 and -3 in rheumatoid arthritis synovial fibroblasts. *Rheumatol. Int.* **2008**, *29*, 23–29.
163. Lee, J.H.; Chung, J.H.; Cho, K.H. The effects of epigallocatechin-3-gallate on extracellular matrix metabolism. *J. Dermatol. Sci.* **2005**, *40*, 195–204.

164. Cheng, X.W.; Kuzuya, M.; Kanda, S.; Maeda, K.; Sasaki, T.; Wang, Q.L.; Tamaya-Mori, N.; Shibata, T.; Iguchi, A. Epigallocatechin-3-gallate binding to MMP-2 inhibits gelatinolytic activity without influencing the attachment to extracellular matrix proteins but enhances MMP-2 binding to TIMP-2. *Arch. Biochem. Biophys.* **2003**, *415*, 126–132.
165. Shakibaei, M.; John, T.; Schulze-Tanzil, G.; Lehmann, I.; Mobasheri, A. Suppression of NF-kappaB activation by curcumin leads to inhibition of expression of cyclo-oxygenase-2 and matrix metalloproteinase-9 in human articular chondrocytes: Implications for the treatment of osteoarthritis. *Biochem. Pharmacol.* **2007**, *73*, 1434–1445.
166. Clutterbuck, A.L.; Mobasheri, A.; Shakibaei, M.; Allaway, D.; Harris, P. Interleukin-1beta-induced extracellular matrix degradation and glycosaminoglycan release is inhibited by curcumin in an explant model of cartilage inflammation. *Ann. N. Y. Acad. Sci.* **2009**, *1171*, 428–435.
167. Buhrmann, C.; Mobasheri, A.; Busch, F.; Aldinger, C.; Stahlmann, R.; Montaseri, A.; Shakibaei, M. Curcumin modulates nuclear factor kappaB (NF-kappaB)-mediated inflammation in human tenocytes *in vitro*: Role of the phosphatidylinositol 3-kinase/Akt pathway. *J. Biol. Chem.* **2011**, *286*, 28556–28566.

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