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COMPLEMENTARY AND ALTERNATIVE MEDICINE (S KOLASINSKI, SECTION EDITOR)

Natural Products for Promoting Joint Health and Managing Osteoarthritis

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Abstract

Purpose of Review Osteoarthritis, the most common joint disease, is associated with substantial medical costs, lost productivity, and reduced quality of life. However, available pharmaceutical treatments have limitations in terms of efficacy and long-term safety.

Recent Findings In vitro evidence suggests that some natural products may possess anti-inflammatory and anti-oxidative properties and may inhibit the release of key osteoarthritis-related cytokines. There is, therefore, ongoing interest in identifying natural products that safely promote joint health and treat osteoarthritis. Numerous plant extracts, including curcumin, *Boswellia* extract, and pycnogenol, have shown effect sizes (ES) for reducing pain and functional disability larger than those observed with analgesics and products such as glucosamine and chondroitin. The ES for methylsulfonylmethane and avocado/soybean unsaponifiables are also considered to be clinically relevant.

Summary Data from a small number of studies using natural products for treating osteoarthritis are promising but require confirmation in further well-designed clinical trials.

Keywords Osteoarthritis · Plant extracts · Curcumin · Pycnogenol · *Boswellia serrata* extract

Introduction

The prevalence of osteoarthritis (OA) of the knee, hip, and hand has been estimated at 20% to 30% in the adult population [1]. Knee OA is the most common form [2]; its prevalence increases throughout the lifespan [2, 3]. Globally, knee and hip OA were estimated to be the 11th greatest contributors to years of life lived with disability in 2010 [4]. Estimated monthly productivity and medical costs related to knee OA were estimated to be €871/patient in the Netherlands, with the loss in productivity primarily driven by painful symptoms [5]. Overall, currently available long-term pharmacotherapeutic treatments available to those with OA offer limited therapeutic benefit, potentially increasing the disease's negative impact [6].

As with any disease, identifying novel treatment options for managing OA and promoting joint health requires an understanding of the underlying biology that leads to the development of the observed symptoms. The pathophysiology of the cartilage degradation central to developing OA is multifactorial but related to the presence of pro-inflammatory cytokines and oxidative stress, which can be exacerbated by the presence of metabolic comorbidities (e.g., obesity, diabetes) [7]. Notably, "inflammaging," chronic low-grade inflammation associated with aging, is the result of a disparity between pro- and anti-inflammatory processes and has been linked to age-related chronic conditions, including OA [8]. Osteoblasts from subchondral bone in OA have an altered pro-inflammatory phenotype, with increased production of alkaline phosphatase, osteocalcin, transforming growth factor-β1

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(TGF-β1), insulin-like growth factor-1 (IGF-1), urokinase plasminogen activator, prostaglandins, cyclooxygenase (COX)-2, and interleukin-6 (IL-6) [9, 10]. Articular cartilage, comprised of chondrocytes and an extracellular matrix (ECM), protects opposing bones of diarthrodial joints [7]. Because chondrocytes maintain the integrity of articular cartilage, when they are damaged or lost (e.g., through senescence and apoptosis), the homeostasis of articular cartilage is compromised, leading to the development of OA [7]. The ECM is made up of proteoglycans, collagens, and other components responsible for maintaining the biomechanical properties of articular cartilage [7]. Proteoglycans attract cations into the ECM, and water is osmotically obliged to follow, which increases resistance to compression, while collagens are fibrous proteins that protect cartilage from biomechanical stress and act as a meshwork for entrapping large and small proteoglycans [7]. The predominant form of collagen is type II, which contributes to the tensile strength of articular cartilage [11]. In OA, synovial membrane displays a spectrum of changes including marked hyperplasia of the lining layer, with a dense cellular infiltrate composed largely of lymphocytes and monocytes, through to a synovial membrane that is thickened by fibrotic tissue [12, 13]. Overloaded subchondral bone is thickened as a result of abnormal bone cell metabolism. Further, microfractures and newly formed vessels constitute exchange routes between bone and cartilage [12–14].

Pain is the primary OA symptom and is linked to structural joint changes including synovitis, joint effusion, cartilage damage, and bone attrition [12]. In addition to pain, which when persistent produces psychological distress and physical deconditioning (e.g., kinesiophobia, disability, sedentarity), other symptoms of OA include stiffness, joint crunching (crepitus) and deformity, and swelling [15, 16]. The main risk factors for developing OA include older age, female sex, and increased body mass index, and the negative impact of OA can be exacerbated by comorbidities, in particular, metabolic symptoms [1, 17]. Based on a meta-analysis, metabolic syndrome (MetS; i.e., obesity, hypertension, dyslipidemia, diabetes) significantly increases the risk of knee OA [17]. These metabolic effects increase inflammation and lead to a consequent immune response, exacerbating OA symptoms and the impact on joint and bone [18]. MetS is associated with a poorer long-term prognosis for OA [19–23]. The factors underlying the relationship between OA and MetS suggest a role for the pro-inflammatory environment and increased immune function related to each condition, but additional research is necessary to elucidate this inter-relationship [24–26]. Taken together, it appears that nutritional factors may have a preventive effect in and/or impact the long-term prognosis of OA [27].

A recent literature review and meta-analysis conducted by Liu et al. (2018) [28, 29] reported that a number of natural products produced clinically important effect sizes (ES) of − 1.2 to − 1.6 in randomized, controlled trials (RCTs), that exceed what has been observed with traditional OA treatments such as glucosamine and chondroitin, which showed no or small effects (ES = − 0.28 to − 0.34). An ES < 0.3 is regarded as small; 0.3–0.8 is moderate, and > 0.8 is a large effect [28, 29]. Therefore, this narrative review was developed to describe these products in the context of the current OA therapeutic landscape. Searches of the PubMed and Cochrane databases were initially conducted in October and November 2017 to identify resources that provide an overview of current OA treatment options and describe the science supporting use of these natural products. Search terms and limitations varied between products and databases, but an emphasis was placed on RCTs, systematic reviews, meta-analyses, and treatment guidelines. Additionally, preclinical data were included to support the proposed mechanism of action of these products.

The OA Therapeutic Landscape

Several organizations have developed guidelines for non-surgical management of OA [30–32]. Osteoarthritis Research Society International (OARSI) guidelines include a treatment algorithm for managing knee OA that begins with less-invasive treatments including exercise, self-management, and education and progresses, taking comorbidities into account, to more-specific treatments such as non-steroidal anti-inflammatory drugs (NSAIDs), biomechanical interventions, and intra-articular (IA) corticosteroids [30]. The 2018 American College of Rheumatology (ACR) guidelines are in progress [33], and the current guidelines recommend oral NSAIDs but do not support using glucosamine and chondroitin sulfate for knee or hip OA [31]. European League Against Rheumatism (EULAR) guidelines describe OA treatments including a graduated approach to first educate patients on disease processes and a tailored treatment approach that includes exercise and lifestyle changes followed by oral pharmacological treatment, IA injections, and surgical interventions [32]. A recent meta-analysis reports short-term benefits of land-based exercise including strength and aerobic training and range of motion exercise [30]. There is also evidence that weight loss combined with exercise reduces pain and improves function in knee OA [30, 32].

Pharmacological Treatments

Acetaminophen

Acetaminophen (paracetamol) is an analgesic commonly used to treat OA [30–32], yet the ES on pain in a recent meta-analysis by da Costa et al. (2017) [34] were small (− 0.07 to − 0.18) and overall non-significant ($P = .68$). In another meta-

analysis of pharmacological knee OA treatments by Bannuru et al. (2015) [35], acetaminophen failed to produce clinically relevant reductions in pain. Additionally, acetaminophen is associated with tolerability issues that should be considered. In particular, a meta-analysis associated using acetaminophen at oral doses of 1950–4000 mg/day with a nearly fourfold greater risk of experiencing abnormal liver function tests versus placebo [36]. Therefore, daily acetaminophen doses should not exceed 4 g to avoid potential hepatotoxicity [37]. Other adverse events (AEs) are rare but can include an allergic reaction leading to a rash or swelling [38].

Non-steroidal Anti-inflammatory Drugs

NSAIDs are regularly recommended for treating OA but not in those with comorbid conditions that can be exacerbated by the established safety issues observed with this class [30–32]. The non-selective COX inhibitor diclofenac at the maximum daily dose of 150 mg/d was the only NSAID shown in the da Costa et al. meta-analysis to produce statistically significant ES on pain (− 0.57; 95% CI − 0.69, − 0.45) and physical functioning (− 0.51; 95% CI − 0.65, − 0.37) [34]. Because NSAIDs are associated with significant gastrointestinal, cardiovascular, and renal AEs, especially at higher doses and over extended periods, they should not be used in individuals with comorbidities in these systems [30]. To limit systemic exposure and reduce the risk for NSAID-related AEs, topical formulations have been developed and are recommended for specific types of OA (e.g., hand, knee) [30–32, 39]. A Cochrane database review by Derry et al. indicated that topical diclofenac and ketoprofen are effective in reducing knee OA-related pain, with ES similar to oral NSAIDs [39].

Intra-articular Injections

IA corticosteroid injections are recommended based on location (e.g., in the knee, but not the hand) and following an incomplete response to less-invasive options [30–32]. A meta-analysis conducted by da Costa et al. [40] indicated that using IA corticosteroids in knee OA produced moderate pain reductions (standard mean difference [SMD] − 0.40; 95% CI − 0.58, − 0.22) and small improvements in physical functioning. Recommendations for using IA hyaluronic acid (HA) are not as consistent, and a meta-analysis by Rutjes et al. [41] reported that IA HA produces a nearly negligible effect on pain from knee OA but carries a significant risk for AEs. However, a meta-analysis of pharmacologic treatments for knee OA conducted by Bannuru et al. (2015) [35] indicated that IA corticosteroids and HA were more effective than oral treatments; still, the authors warned of a high placebo response with these interventions.

Natural Products for Treating Osteoarthritis

Due to the small-to-moderate ES seen with more traditional pharmaceutical agents and supplements, there is continued high interest in identifying other natural products that safely promote joint health [28, 29, 42]. This was exemplified by a meta-analysis published by Liu et al. [29] evaluating oral supplements formulated with natural components. This analysis demonstrated a strong effect, with ES > 1 for pain and/or functioning with certain products, including methylsulfonylmethane (MSM), curcumin from turmeric (*Curcuma longa*), *Boswellia serrata* (*B. serrata*), and pycnogenol. Willow bark, *B. serrata*, curcumin, and pycnogenol are plant extracts, and curcumin and pycnogenol are specifically polyphenols [28, 42] that can have low bioavailability and require optimized formulations [43]. The ES for each of these products as described by Liu et al. are summarized in Table 1 for comparison; individual studies included in the meta-analysis are cited by Liu et al. [29]. As a class, polyphenols are known to possess anti-inflammatory properties, making them potentially of interest for OA, but as the evidence for these ingredients continues to grow, other properties have been identified, such as anti-oxidation [42, 44].

Glucosamine and/or chondroitin, and avocado/soybean unsaponifiables (ASUs) are often used for managing OA. Some of these products are classified as drugs in the

Table 1 Results of a review of dietary supplements for osteoarthritis

Ingredient	Pain	Functioning
Glucosamine sulfate/hydrochloride		
Effect size (95% CI)	− 0.28 (− 0.52, − 0.04)	− 0.45 (− 0.73, − 0.17)
Chondroitin sulfate		
Effect size (95% CI)	− 0.34 (− 0.49, − 0.19)	− 0.36 (− 0.58, − 0.13)
Vitamin D[a]		
Effect size (95% CI)	− 0.19 (− 0.31, − 0.06)	− 0.36 (− 0.61, − 0.11)
Willow bark extract		
Effect size (95% CI)	− 0.29 (− 0.62, 0.04)	− 0.24 (− 0.55, 0.07)
Methylsulfonylmethane		
Effect size (95% CI)	− 0.47 (− 0.80, − 0.14)	− 1.10 (− 1.81, − 0.38)
Avocado/soybean unsaponifiables		
Effect size (95% CI)	− 0.57 (− 0.95, − 0.19)	− 0.48 (− 0.69, − 0.28)
Curcumin		
Effect size (95% CI)	− 1.19 (− 1.93, − 0.45)	− 1.13 (− 1.80, − 0.46)
Boswellia serrata extract		
Effect size (95% CI)	− 1.61 (− 2.10, − 1.13)	− 1.15 (− 1.63, − 0.68)
Pycnogenol		
Effect size (95% CI)	− 1.21 (− 1.53, − 0.89)	− 1.84 (− 2.32, − 1.35)

From [29]

CI confidence interval

[a] Long-term

European Union and have mixed recommendations in OA guidelines [30–32, 45]. These products are government regulated and prescribed by physicians; they include specific formulations that have been tested and are extracted using patented processes (e.g., an ASU developed by Expanscience Laboratories) [42]. However, in the USA, ASUs, including Avoca ASU (Nutramax Laboratories, Inc.) and Maximize ASU (Maximum International, USA), are classified as dietary supplements and not strictly regulated [46]. Regulatory procedures are important for determining the effectiveness of a given product, as the formulations have been standardized and evaluated independently [46]. A study examining the effectiveness of chondroitin sulfate noted that achieving accurate and reproducible results requires using a pharmaceutical-grade product with high specificity, purity, and well-known physiochemical properties and structure [47]. Further, the label declaration of purity and its precise formulation are critical, and researchers should take steps to ensure identity and purity before testing [48].

Glucosamine

The amino sugar glucosamine is found naturally in the body, involved with producing lipids and glycosylated protein, and highly expressed in articular cartilage and synovial fluid [49]. A meta-analysis conducted by Lee et al. [50] reported that glucosamine sulfate provided a small-to-moderate effect over 3 years on progressive articular degeneration in knee OA, as measured using joint space narrowing. A Cochrane review of glucosamine trials reported improvements in OA-related pain and functional impairment, in particular, with a crystalline glucosamine sulfate formulation marketed by Rotta that is classified as a nutraceutical [51, 52]. However, analyses that included studies using other glucosamine formulations did not observe any benefit compared with placebo [51]. A meta-analysis conducted by Eriksen et al. [53] that included nutraceuticals reported a measurable reduction in pain with glucosamine but questioned the clinical relevance (ES − 0.51; 95% CI − 0.72, − 0.30). Moreover, the authors reported significant heterogeneity and a risk for bias due to poor study quality and industry sponsorship. The analysis also indicated that the characteristics of the specific glucosamine formulation being evaluated can impact the results. The Liu et al. [28, 29] meta-analysis included 17 trials and reported small ES on pain (− 0.28; 95% CI − 0.52, − 0.04), disability improvement (− 0.45; 95% CI − 0.73, − 0.17), and joint space narrowing (− 0.19; 95% CI − 0.48, 0.09) for glucosamine sulfate/hydrochloride supplements and nutraceuticals, which is consistent with earlier results. The available evidence suggests that pharmaceutical-grade products, as opposed to dietary supplements, should be used due to potential concerns with the quality of the glucosamine used [54].

Chondroitin

Chondroitin is a naturally occurring glycosaminoglycan and a component of articular cartilage that is used alone or combined with glucosamine in OA [54–56]. A Cochrane review by Singh et al. [55] reported that chondroitin alone produced medium to moderate pain reductions (SMD − 0.51; 95% CI − 0.74, − 0.23); the SMD for chondroitin with/without glucosamine was slightly higher (− 0.63; 95% CI − 0.93, − 0.33). A meta-analysis conducted by Richy et al. [57] reported that glucosamine or chondroitin positively impacted pain (ES − 0.45; 95% CI − 0.33, − 0.57; $P < .001$) and glucosamine positively impacted joint space narrowing (ES − 0.41; 95% CI − 0.21, − 0.60; $P < .001$), but a more recent meta-analysis by Wandel et al. [58] reported no effect with glucosamine, chondroitin, or their combination (pain: ES − 0.13 to − 0.19; joint space narrowing: ES 0.00 to − 0.16). Based on the Liu et al. [29] meta-analysis, the short-term use of chondroitin sulfate produced an ES of − 0.34 (95% CI − 0.49, − 0.19) on pain across nine RCTs and − 0.36 (95% CI − 0.58, − 0.13) on functioning using data from eight RCTs. Long-term use in four trials produced an ES of − 0.30 (95% CI − 0.42, − 0.17) on joint space narrowing. The quality of evidence for these studies was generally low to moderate.

The small-to-moderate ES seen in these meta-analyses of glucosamine and chondroitin RCTs reflect the fact that there are a number of positive and negative studies that have evaluated these products. Although some individual studies suggest that glucosamine combined with chondroitin may have advantages over each product individually due to potential synergistic effects [54], the meta-analysis by Wandel et al. found that there was no evidence of benefit with this combination [58].

In summary, depending of the quality of the clinical trials and the formulation tested, chondroitin and/or glucosamine is effective or not for individual patients. This underlines the importance for researchers and clinicians to control the product formulation, scientific background, and methodological quality of the clinical trials supporting the efficacy of glucosamine and chondroitin sulfate products. In the clinical setting, the efficacy of glucosamine and chondroitin sulfate products should be monitored every 6 months at the individual level. If no clinically significant effect is reported, the physician should consider changing the treatment regimen.

Avocado/Soybean Unsaponifiables

ASUs are classified as either drugs or supplements and contain various components including plant sterols (e.g., phytosterols, β-sitosterols), fat-soluble vitamins, and possibly, furan fatty acids that may benefit joint health [9, 46]. In vitro and in vivo data suggest that ASUs enhance collagen synthesis, delay joint damage, and reduce inflammatory and catabolic mediators (e.g., ILs, COX-2, prostaglandins). Although further studies are required to

determine the mechanisms by which they exert their effects, ASUs also have anti-inflammatory, chondroprotective, anabolic, and anti-catabolic properties, and they reduce acute pain and prevent OA symptom progression [46]. RCTs conducted with ASUs have reported reductions in NSAID use in hip and knee OA [59], positive effects on hip and knee OA pain and functioning [60], reduced knee OA severity (based on the Lequesne index) [61], and reduced joint space narrowing in hip OA in a subgroup with advanced joint space narrowing [62]. In the Liu et al. [29] meta-analysis, short-term ASU use (two studies) produced ES of − 0.57 (95% CI − 0.95, − 0.19) on pain and − 0.48 (95% CI − 0.69, − 0.28) on functioning. The ES on joint space narrowing was − 0.05 (95% CI − 0.23, 0.14) with long-term ASU use. Notably, these studies have primarily been conducted with a proprietary product developed by Expanscience.

Methylsulfonylmethane

MSM is an organosulfur that occurs in numerous forms (e.g., dimethyl sulfone, methyl sulfone, dimethyl sulfoxide [DMSO]) and has anti-inflammatory and anti-oxidative properties [63]. In a controlled trial that evaluated exercise-induced cytokine release, MSM reduced leukocyte apoptosis by inhibiting IL-6, -8, and -17 [64]. Furthermore, using an animal model of knee OA, MSM decreased cartilage degeneration, suggesting that MSM could potentially slow the progression of OA [65]. The Liu et al. [29] meta-analysis reported that across three studies, MSM produced ES of − 0.47 (95% CI − 0.80, − 0.14) and − 1.10 (95% CI − 1.81, − 0.38) on pain and functioning, respectively, in knee OA; however, the quality of evidence was low and very low, respectively. A separate meta-analysis conducted of two trials with MSM and DMSO in knee OA reported ES versus placebo of 3.53 and 2.06, respectively, for joint pain, although this was not thought to be clinically relevant [66].

Willow Bark Extract

Salix extract (willow bark extract) has been shown to be a potent antioxidant in vitro and slowed the development of OA using an animal model by reducing inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, IL-1β, and IL-6) and nitric oxide [NO] production [67]. A systematic review conducted by Vlachojannis et al. [68] reported that willow bark extract alleviated lower back pain, and in the Liu et al. [29] meta-analysis, the ES on pain across two studies was − 0.29 (95% CI − 0.62, 0.04) and − 0.24 (95% CI − 0.55, 0.07) on improving physical functioning, with a low quality of evidence. Willow bark extract contains a bioactive compound related to aspirin (i.e., salicin; a prodrug that is metabolized to salicylate derivatives), which is thought to be responsible for its analgesic and anti-inflammatory properties [69, 70]. However, the mechanism of action of willow bark extract is likely driven by additional factors, in part because the concentration of salicylate derivatives may be too low to produce the observed level of analgesia [70]. Therefore, the polyphenols, flavonoids, and proanthocyanidins that are also constituents of willow bark extract likely contribute to its pharmacologic activity, with effects on COX-1, COX-2, 5-lipoxygenase (5-LOX), human leucocyte elastase, TNF-α, IL-1, IL-6, NO synthesis, and apoptosis [69, 71, 72].

Curcumin

Curcumin (diferuloylmethane) is the principal curcuminoid extract of the *C longa* (turmeric) root and has a long history of use as a cooking spice (primarily in curries), but it is also used in traditional Chinese Ayurvedic medicine, primarily for treating indigestion [73]. The mechanism of action of curcumin in OA is based on its anti-inflammatory properties; however, additional relevant mechanisms have been identified [73]. The anti-inflammatory effect of curcumin is related to the direct inhibition of 5-LOX and nuclear factor-kappa B (NF-κβ) and indirect inhibition of phospholipase A_2 and COX-2, as well as cell viability, anti-oxidative, and anti-catabolic effects [73]. Curcumin is an inhibitor of IL-1β, -6, and -8, COX-2, PGE_2, and metalloproteinase (MMP)-3 gene expression and acts as a scavenger of reactive oxygen and nitrogen species, effects that have been observed in various pre-clinical models [73, 74].

The meta-analysis conducted by Liu et al. [29] reported a pooled ES on pain relief for curcumin using data from two studies of − 1.19 (95% CI − 1.93, − 0.45), but the quality of evidence was very low. A meta-analysis of different turmeric derivatives including curcumin reported significant ES on a visual analog scale for pain (− 2.04; 95% CI − 2.85, − 1.24; $P < .00001$) and on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (− 15.36; 95% CI − 26.94, − 3.77; $P = .009$) versus placebo and equivalent effects versus analgesics (− 1.89; 95% CI − 4.13, 0.35; $P = .10$) [75]. The bioavailability of curcumin is a major challenge because it is inherently low in humans [43]. A meta-analysis by Sahebkar et al. [43] reported that the use of adjuvants such as piperine, liposomal delivery systems, phospholipid complexes of curcumin, or polysorbate as an emulsifier to improve curcumin bioavailability had a positive influence on the overall analgesic ES of curcuminoids in humans.

Boswellia serrata

The extract of the gum resin of *B. serrata* (i.e., Indian frankincense) is thought to have two principal pharmacologically active compounds: 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid [76]. *B. serrata* has been shown to have anti-inflammatory properties that are driven by inhibiting 5-LOX, MMP-3, and TNF-α [76, 77]. Using an in vitro articular

cartilage model, *B. serrata* has been shown to protect from IL-1α and human recombinant oncostatin M-mediated damage, an effect driven by inhibiting MMP-9 and MMP-13 transcription and MMP-9 synthesis and reducing NO, PGE_2, and COX-2 [78]. Additionally, through the use of a mechanical pain model, *B. serrata* was shown to significantly increase pain threshold and tolerance compared with placebo [79]. In the Liu et al. [29] meta-analysis (three studies), the ES on pain relief and improvement in disability for *B. serrata* were − 1.61 (95% CI − 2.10, − 1.13) and − 1.15 (95% CI − 1.63, − 0.68), respectively. The GRADE ratings ranged from low to very low quality of evidence.

Pycnogenol

Pycnogenol (French maritime pine bark extract) contains phenolic acids, taxifolin, and procyanidins, which produce various biological effects [42]. Pycnogenol has been shown to have antioxidant and anti-inflammatory properties, including reducing C-reactive protein and inhibiting MMP-9 and NF-κβ signaling pathways [42, 80, 81]. Taken orally, pycnogenol increases expression of HA and type II collagen messenger RNA in the skin [82], and the metabolites of pycnogenol accumulate in synovial fluid of OA patients [83]. The Liu et al. [29] meta-analysis reported pooled ES for pycnogenol from two studies of − 1.21 (95% CI − 1.53, − 0.89) and − 1.84 (95% CI − 2.32, − 1.35) on pain relief and disability, respectively; the quality of evidence was moderate. Although pycnogenol has been evaluated for a number of chronic medical conditions, including OA, a Cochrane database review reported that it has not been studied widely enough and there is potential bias in the conducted studies, precluding a recommendation for its use in chronic conditions [84].

Discussion

This literature review suggests that current evidence does not fully support the use of pharmaceutically based analgesics (i.e., acetaminophen, NSAIDs) for OA due to small ES and potential safety concerns (Table 2). Similarly, although glucosamine sulfate and chondroitin sulfate are widely used for reducing pain and/or improving functional impairment associated with OA, the ES are relatively small (≤ − 0.45). The ES for pain and functioning with MSM and ASUs were reported to be approximately ≥ −0.50 in the Liu meta-analysis [29]. The ES on pain and functioning for three polyphenols (i.e., curcumin [pain only], *B. serrata*, and pycnogenol) ranged from − 1.2 to − 1.8, suggesting benefits beyond what is observed with analgesics, glucosamine, and chondroitin. However, despite these promising results, it is important to note that these findings are based on small populations [29]. Furthermore, the quality of the majority of the studies included in these meta-analyses was moderate to low [28, 29], and as with all meta-analyses, there is the potential for introducing bias with study selection [89]. As a result, high-quality controlled trials are necessary to more clearly establish these effects.

Table 2 Overview of commonly utilized and emerging treatments for osteoarthritis

Treatment	Mechanism of Action
Pharmaceuticals	
Acetaminophen	Analgesic [30]
NSAIDs	Anti-inflammatory [39]
Symptomatic slow-acting drugs for osteoarthritis[a]	
Diacerein	Analgesic [85–87] Cartilage synthesis [87, 88] Anti-inflammatory [88]
Chondroitin sulfate	Cartilage synthesis [50, 55, 58]
Glucosamine	Cartilage synthesis [50, 58]
ASUs	Anti-inflammatory [46]
Dietary supplements and plant extracts	
Willow bark extract	Analgesic [69, 70] Anti-inflammatory [69, 70]
MSM	Anti-inflammatory [63] Anti-oxidative [63]
Curcumin	Anti-inflammatory [73]
Boswellia serrata	Anti-inflammatory [76, 77]
Pycnogenol	Anti-inflammatory [42, 80, 81] Anti-oxidative [42, 81]

[a] Some symptomatic slow-acting drugs for osteoarthritis are classified as supplements in the USA

ASUs avocado/soybean unsaponifiables, *MSM* methylsulfonylmethane, *NSAIDS* non-steroidal anti-inflammatory drugs

This literature review provides some insights into additional research areas. For example, it may be worthwhile examining the effects of glucosamine and chondroitin in relation to *B. serrata* and pycnogenol for pain relief and functional impairment and curcumin for pain relief to determine whether they truly offer superior benefits. Furthermore, the differing mechanisms of action of these treatments may prove to be relevant for particular patient phenotypes. Glucosamine stimulates glycosaminoglycan synthesis, while polyphenols (e.g., *B. serrata*, pycnogenol, curcumin) possess anti-inflammatory properties, inhibiting the release of key OA-related cytokines that exacerbate articular degeneration. Future studies could combine ingredients with complimentary mechanisms of action, allowing for the evaluation of potential synergistic effects.

Due to wide variability in products that include the natural ingredients discussed in this review, the sources need to be considered when evaluating their potential benefits. To that end, it is important that companies manufacturing these products verify the raw materials used and not rely solely on the suppliers' certificates

of analysis [90]. Additionally, there is the potential for inconsistencies between the ingredients used in pre-clinical studies compared with RCTs and those that are available to consumers. The source of the ingredients used in RCTs should therefore be standardized, and ultimately, companies manufacturing these products must verify the raw materials and consider third-party testing for potency.

Conclusions

In summary, the literature reviewed here indicates that current pharmaceutical treatments frequently used to manage OA do not provide optimal levels of relief; therefore, additional therapeutic options are needed that can more effectively and safely provide relief to those with OA. Curcumin, *B. serrata* extract, and pycnogenol are plant extracts that have promising pre-clinical and clinical trial data indicating their potential to reduce OA-related pain and functional disability. Additional clinical trials with these ingredients (individually or in combination) are necessary to more fully establish their usefulness.

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Compliance with Ethical Standards

Conflict of Interest YH is the founder of Artialis SA, a spin-off company of the University of Liège. He has also received fees from Bepharbel, Expansciences, Flexion, GSK, Ibsa, KiOmed Pharma SA (formerly Synolyne Pharma SA), Labhra, Nestle, and Tilman SA.

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