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Review

Potential complementary and/or synergistic effects of curcumin and boswellic acids for management of osteoarthritis

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***Abstract*:** For several thousand years (~4000) *Boswellia serrata* and *Curcuma longa* have been used in Aryuvedic medicine for treatment of various illnesses, including asthma, peptic ulcers, and rheumatoid arthritis, all of which are mediated through pathways associated with inflammation and pain. Although the *in vivo* pharmacology of both these natural ingredients is difficult to study because of poor bioavailability, *in vitro* data suggest that both influence gene expression mediated through nuclear factor kappa B (NF-κB). Therefore, the activity of pathways associated with inflammation (including NF-κB and lipoxygenase- and cyclooxygenase-mediated reduction in leukotrienes/prostaglandins) and those involved in matrix degradation and apoptosis are reduced, resulting in a reduction in pain. Additive activity of boswellic acids and curcumin was observed in preclinical models and synergism was suggested in clinical trials for the management of osteoarthritis (OA) pain. Overall, studies of these natural ingredients, alone or in combination, revealed that these extracts relieved pain from OA and other inflammatory conditions. This may present an opportunity to improve patient care by offering alternatives for patients and physicians, and potentially reducing nonsteroidal anti-inflammatory or other pharmacologic agent use. Additional research is needed on the effects of curcumin on the microbiome and the influence of intestinal metabolism on the activity of curcuminoids to further enhance formulations to ensure sufficient anti-inflammatory and antinociceptive activity. This narrative review includes evidence from *in vitro* and preclinical studies, and clinical trials that have evaluated the mechanism of action, pharmacokinetics, efficacy, and safety of curcumin and boswellic acids individually and in combination for the management of OA pain.

Keywords: *Boswellia serrata*, complementary and alternative medicine, curcuma longa, nonsteroidal anti-inflammatory drugs (NSAIDs), osteoarthritis (OA), pain management, phytotherapy

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Introduction

Osteoarthritis (OA) is a leading cause of disability in older adults, with over 500 million cases globally in 2019.[1,2] Management of musculoskeletal pain and OA often includes pharmacologic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are broadly effective but are associated with safety concerns, including gastrointestinal, hepatic, and cardiovascular adverse events.[3–5] Most patients with OA also have other comorbidities, such as diabetes, hypertension, and dyslipidemia, which complicates the identification of suitable treatment options and can further increase inflammation, leading to disease progression.[6,7] Therefore, additional safe and effective alternative pain relief options are needed.

Patients and physicians are beginning to explore complementary and prophylactic therapies that may offer both symptom relief and a favorable safety profile.[8,9] In addition, patients and physicians want interventions that (1) eventually become prophylactic options to help treat the root cause of the condition, (2) decrease inflammation and pain, which subsequently reduces damage, (3) have more favorable adverse-effect profiles, and (4) can be taken long term. Natural ingredients have the potential to fill these needs and could minimize

NSAID exposure and associated adverse events.[10–13] Furthermore, *in vitro* bioassays suggest that the use of natural ingredients in combination with NSAIDs could provide a more favorable safety/risk–benefit profile;[14] molecular studies investigating the combination at the chemical level are ongoing. Some natural ingredients can be part of the solution in the approach to personalized pain medicine; however, many studies described in the literature did not combine NSAIDs and natural ingredients in the comparator arm of their trials.[15–17]

Two natural ingredients, *Curcuma longa* and *Boswellia serrata*, have been used for several thousand years (~4000) for the treatment of inflammatory, pain-related, and degenerative disorders.[18–20] Synergy of the beneficial anti-inflammatory and antinociceptive effects from both curcumin and boswellic acids has been suggested both *in vitro* and *in vivo*, and pharmacokinetic and clinical studies in humans reported no major safety concerns when these two natural ingredients are combined.[21–24] Therefore, identifying the appropriate dose and formulation for the combination of these natural ingredients for complementary and/or synergistic targeting of OA and musculoskeletal pain is of interest. In addition, identification of the appropriate dosing in combination with NSAIDs can increase the number of pain treatment options for patients and provide an improved risk profile.

The objective of this narrative review was to examine the efficacy and safety of curcumin and boswellic acids alone to support their use in combination to treat and manage musculoskeletal pain in patients with OA. These two natural ingredients were recently investigated for many different biological conditions, such as OA and cancer, and those findings are relevant for identifying the affected molecular pathways. In addition, individual complementary and prophylactic therapies were found to be non-inferior to NSAIDs in clinical trials.[10,12,13,25–27] The combination of natural ingredients may prove to be as effective as, or more effective than, pharmacologic agents due to their unique mode of action and complementary and/or synergistic effects.

Curcumin mechanism of action

Curcumin, the main component of polyphenolic compounds called curcuminoids, is extracted from turmeric, a product of the *Curcuma longa* plant; additional curcuminoid components include demethoxycurcumin and bisdemethoxycurcumin (Figure 1).[28] The evidence for the mechanism of action of curcumin is derived from *in vitro* and *in vivo* studies, including cell lines representative of synovial cells and chondrocytes, rat and mouse models, and clinical samples from patients with OA and healthy volunteers. Curcumin downregulates the cyclooxygenase-2 (COX-2) pathway, reducing the production of prostaglandins associated with inflammation (Figure 2).[29,30] Curcumin also downregulates and directly inhibits lipoxygenase (LOX) and downregulates inducible nitric oxide synthase, mitogen-activated protein kinases, and Janus kinases, which are associated with inflammatory processes.[29,31] Downstream effects of curcumin through these pathways include inhibition of nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB)-mediated gene expression of cytokines, including reduced production of tumor necrosis factor-alpha (TNF-α), interleukins (ILs-1, -2, -6, -8, and -12), monocyte chemoattractant protein (MCP), migration inhibitory protein, prostaglandin E_2 (PGE_2), matrix metalloproteinase (MMP)-2,-3,-9, inflammasome NLRP3, and reactive oxygen species.[28,32–38] IL-10, a cytokine associated with reducing inflammation, is increased by curcumin supplementation in various inflammatory diseases, and the anti-inflammatory activity of IL-10 is enhanced through blocking pathways associated with inflammation.[39] For pain, curcumin's antinociceptive effect is mediated by IL-10 *via* augmentation of Nrf2 and Cu/Zn superoxide dismutase.[39] Nrf2/ARE is a key pathway in curcumin-mediated protection against inflammation and oxidative stress in chondrocytes.[40]

Curcumin also was shown to protect human temporomandibular joint chondrocytes from matrix degradation.[40] Curcumin has potential effects on Toll-like receptor 4 (TLR4) in models of OA.[41,42] A study of intra-articular administration of curcumin in the right knee of a rat with OA (classical model of OA induced by anterior cruciate ligament transection), showed that curcumin repressed lipopolysaccharide-induced IL-1β and TNF-α secretion from the synovium and inhibited lipopolysaccharide-induced overexpression of TLR4 and downstream NF-κB in cartilage and synovial tissues.[41] Thus, curcumin effectively reduces activity in inflammatory pathways known to be involved with OA pathogenesis.[32] Through reductions in inflammation, OA pain is reduced as well.

Curcuminoids have demonstrated other activities in preclinical studies, including antineoplastic, antifungal, analgesic, antimicrobial, antioxidant,

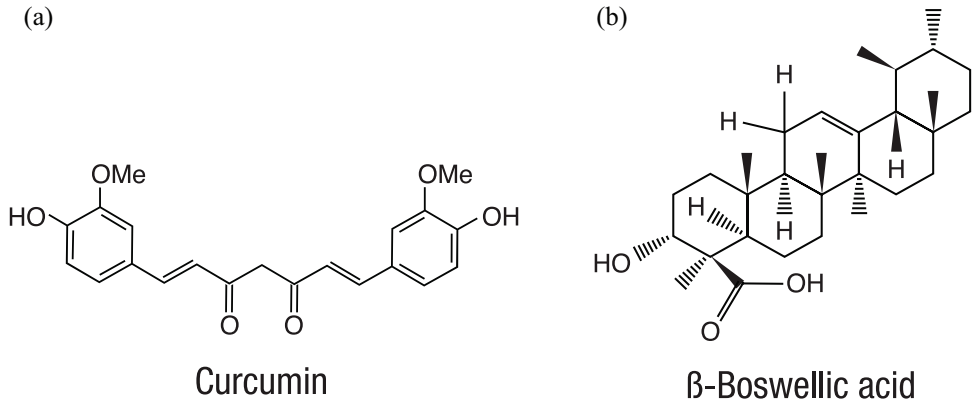

Figure 1. Structure of (a) key curcuminoids and (b) boswellic acids.[43,44]

hepatoprotective, hypoglycemic, immunostimulant, antiasthmatic, and hypercholesterolemic effects.[28,45] Although most of these observations are from *in vitro* studies, the authors hypothesized that the potential universal effect of the curcuminoids on inflammation/oxidative stress occurs through an effect on redox imbalance, which could suggest that curcumin may be a prodrug because it appears to be active in numerous pathways.[46]

This hypothesis also is supported by curcumin's poor bioavailability in humans. Furthermore, the prodrug theory could support the variability observed in different preparations of curcumin; bioactive intermediates from oxidative metabolism of curcumin account for at least some of the observed activity.[46] The biologic effects of curcumin in the gut also may explain its overall anti-inflammatory effects, as CurA from *Escherichia coli* in the human intestine has been shown to produce tetrahydrocurcumin, a metabolite of curcumin that has been shown to be biologically active.[47,48] If the microbial products of curcumin (metabolites), which have yet to be identified, are responsible for the beneficial effects of curcumin, then limited bioavailability or absorption in the small intestine may not be a significant issue. For example, there have been various studies in rats in which tissue or serum malondialdehyde concentrations were lowered by 12–30% when either 100 or 200 mg/kg curcumin was administered before intestinal ischemia reperfusion.[47,49–52] Curcumin has effects on microbiota, intestinal permeability, gut inflammation, oxidative response, anaphylactic reactions to oral allergic food exposure, and bacterial, parasitic, and fungal infections,[47] and it is believed that positive effects on the microbiome may have effects on extra-intestinal disease.[47] Concentrated extracts of curcumin through solvent extraction of turmeric, such as BCM-95 and C3,[53] provide another mechanism for increasing bioavailability. The efficacy of this approach is illustrated by one pharmacokinetic study in healthy volunteers that showed an approximate seven-fold increase in bioavailability with BCM-95 compared with standard curcumin.[54] Overall, the mechanism of action and clinical pharmacology of curcumin *in vivo* need additional research in humans to confirm the *in vitro* data and to address how to achieve effective concentrations of active curcumin metabolites.

Boswellic acids mechanism of action

Boswellia is derived from the gum resin extracts of the Indian olibanum tree, *Boswellia serrata*, which contains a mixture of triterpene acids known as boswellic acids (Figure 1).[45,55]

Two boswellic acids, 11-keto-β-boswellic acid (KBA) and acetyl-11-keto-β-boswellic acid (AKBA), were proposed as the main transducers of pharmacologic effects.[55] Boswellic acids inhibit the 5-LOX pathway, reducing the production of proinflammatory leukotrienes.[56,57] However, no clear correlation has been established between KBA/AKBA plasma concentrations and the effective concentrations for inhibiting 5-LOX, which may be due to the poor absorption of AKBA after oral administration.[55] One approach to increase AKBA bioavailability has been to use concentrated extracts, such as ApresFlex and 5-Loxin, which have between 20% and 30% AKBA, respectively.[58] In a preclinical rat model, ApresFlex showed greater absorption *versus* the same dose of 5-Loxin.[59] Further research into concentrated extracts could provide more insight into the effective concentrations needed to inhibit 5-LOX. Boswellic acids also inhibit COX-2 in the

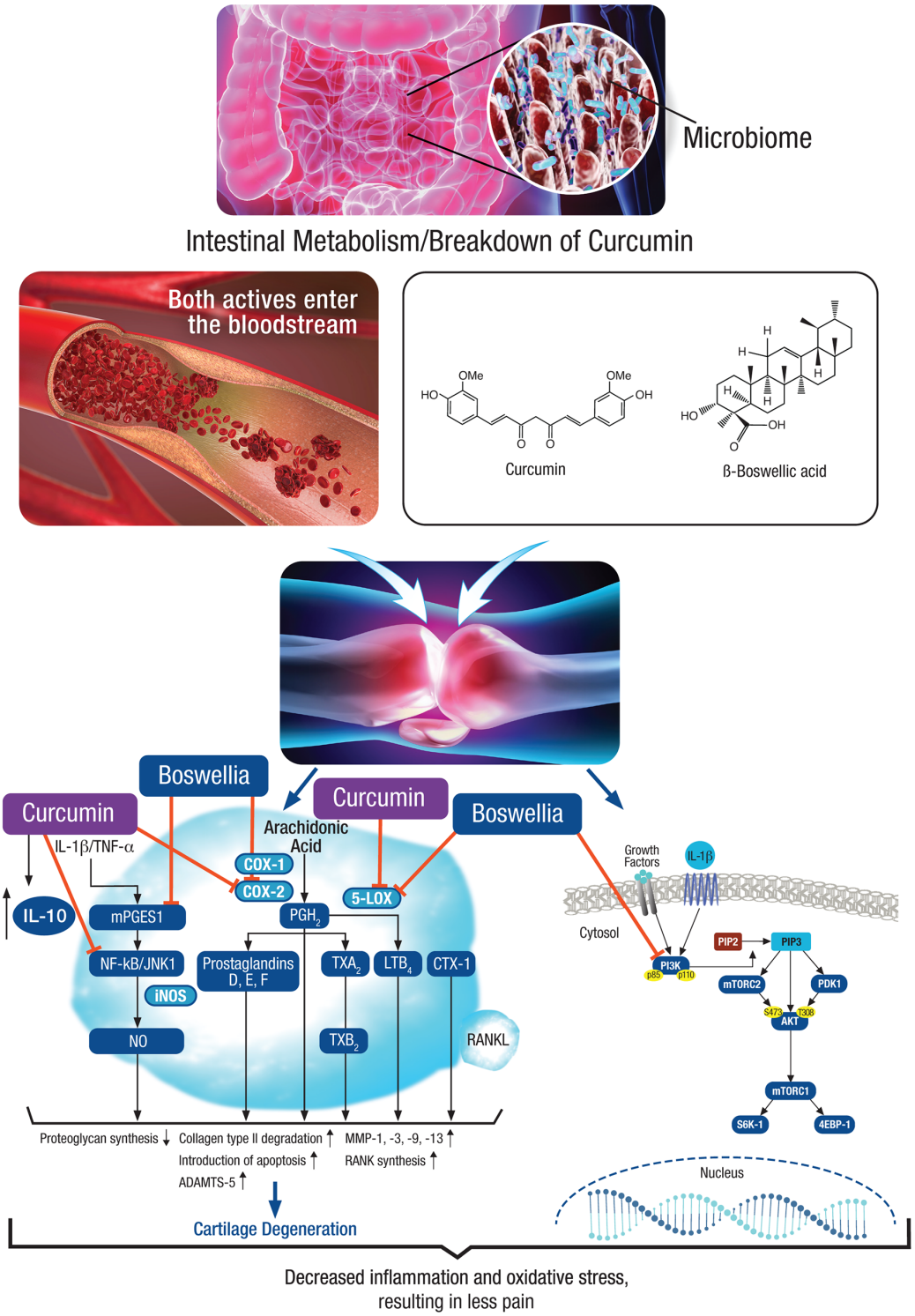

Figure 2. Mechanism of action of curcumin and boswellic acids in osteoarthritis based on *in vitro* study data. 4EBP-1, eukaryotic translation initiation factor 4E-binding protein 1; 5-LOX, 5-lipoxygenase; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AKT, protein kinase B; COX, cyclooxygenase; CTX, carboxy-terminal cross-linking telopeptide of type I collagen; IL, interleukin; iNOS, inducible nitrous oxide synthase; JNK, c-Jun N-terminal kinase; LTB, lymphotoxin-beta; MMP, matrix metalloproteinase; mPGES-1, microsomal prostaglandin E synthase-1; mTORC, mammalian target of rapamycin complex; NF-κB, nuclear factor-kappa B; NO, nitrous oxide; PGH_2, prostaglandin H2; PI3 K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3,4,5 trisphosphate; RANKL, receptor activator of NFκB ligand; S6 K-1, ribosomal protein S6 kinase beta-1; TNF-α, tumor necrosis factor–alpha; TXA_2, thromboxane A2; TXB_2, thromboxane B2.

arachidonic acid pathway, metabolites of which mediate pain and inflammation.[57] COX-2 inhibition decreases prostaglandin H_2 and subsequently PGE_2, which promotes inflammation.[55,57] β-Boswellic acid has shown higher steady-state plasma concentrations in humans than AKBA, which aligns with the *in vitro* IC_{50} values for cathepsin G (catG) and microsomal prostaglandin E synthase-1 (mPGES-1), suggesting an alternative pathway for anti-inflammatory effects.[55] mPGES-1 is likely to be involved in cartilage/matrix homeostasis through mechanosensitive gene induction, and is a potential therapeutic target in OA.[60]

Another pathway implicated in the anti-inflammatory effects of AKBA is NF-κB. In a rat model of osteoporosis, administration of 35 mg/kg AKBA for 42 days resulted in significant improvement in calcium content and bone mineral density ($p < 0.01$ for both) and downregulation of NF-κB and NF-κB-regulated gene expression, suggesting that AKBA has a role in management of postmenopausal osteoporosis through inhibition of osteoclastogenesis.[61]

The PI3K/AKT pathway regulates target genes involved in cancer and OA, and *in vitro* studies with AKBA in these different disease states suggests that there may be a common mechanism of action. Potential anticancer effects of AKBA have been observed in human gastric cancer cell lines through induction of apoptosis, cell cycle arrest, autophagy suppression, and inhibition of cell migration and the PI3K/AKT pathway.[62–65] Anticancer effects were studied in a variety of cell lines and cancer types and have demonstrated dose-dependent responses, the potential to use AKBA as an adjuvant to chemotherapy, and as a promising therapy for non-small cell lung cancer.[62,63,65] Recent *in vitro* and *in vivo* studies have suggested a potential new role of the PI3K/AKT pathway in OA, where inhibition of PI3K/AKT prevents expression of target genes (e.g. TNF-α, IL-6, MMPs, and COX-2) that increase the inflammatory responses and cartilage matrix degradation that lead to OA development.[66–68] Boswellic acids therefore may downregulate inflammation and oxidative stress in OA, thereby reducing cartilage damage and joint pain.

Comorbidities, such as diabetes and obesity, can amplify mechanical and inflammatory pressure on the joints in OA. Boswellic acids act on inflammation in diabetes and other comorbid conditions that make joint pain worse in OA, and may prevent types 1 and 2 diabetes through suppression of the expression of proinflammatory cytokines.[69,70] Additional research is needed to confirm the pharmacodynamics of boswellic acids *in vivo*, similar to curcumin. The safety of boswellic acids has been studied preclinically in primates and rats, with no toxic side effects observed.[45] One of the side effects reported in humans is skin reactions or rashes, but thus far, no serious safety issues have been documented.[71]

Antinociceptive effects of curcumin and boswellic acids

Preclinical OA animal models in mice and rats showed antinociceptive effects of curcumin and boswellic acids *via* topical and oral administration, respectively.[72,73] In the mouse OA model, topical curcumin nanoparticles reduced tactile hypersensitivity in the von Frey test, increased distance traveled, and increased rearing compared with vehicle-treated animals that also had destabilization of the medial meniscus (all $p < 0.05$).[72] This suggests curcumin is effective in relieving pain associated with OA. Additional investigation showed that oral and topical curcumin slowed the progression of OA in the mouse model through decreased cartilage erosion and proteoglycan loss, reduced synovitis and subchondral plate thickness, reduced degradation of type II collagen and aggrecan, and lowered expression of MMP-13 and ADAMTS5 compared with vehicle controls.[72] In the rat OA model, rats treated with boswellic acids improved weight-bearing function measured *via* the von Frey test at day 14 and latency of paw withdrawal at day 15 compared with monoiodoacetate control rats.[73] *In vitro* studies of boswellic acids showed dose-dependent inhibition of 5-LOX activity and strongly inhibited PGE_2 production in lipopolysaccharide-induced peripheral blood mononuclear cells, indicative of inhibition of the COX pathway for inflammatory pain.[73] Furthermore, boswellic acids helped block the harmful effects of proinflammatory cytokines on human chondrocytes in culture.[73] Therefore, there is the potential for both curcumin and boswellic acids to be protective for chondrocytes in OA and for additive benefit in reducing pain in OA. Additional research in humans is needed to confirm the exact mechanism of these natural ingredients in reducing pain in OA.

Curcumin for OA

Data from clinical trials evaluating the efficacy of curcumin for managing OA (Table 1) support

Table 1. Clinical trials of curcumin for OA.

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
Randomized, double-blind, placebo-controlled trial in patients with mild to moderate knee OA[12]	40 (19 received curcumin and 21 received placebo)	500 mg three times daily (70–80% curcumin, 15–25% demethoxycurcumin, and 2.5–6.5% bisdemethoxycurcumin) for 6 weeks Placebo capsules were matched in size and shape	Greater effect of curcumin *versus* placebo on decreased global ($p = 0.001$), pain ($p < 0.001$), and physical function ($p < 0.001$) WOMAC scores and on decreased LPFI ($p = 0.013$) and VAS ($p < 0.001$) scores; higher proportion of patients on curcumin decreased rescue medication *versus* placebo ($p < 0.001$)	Significant decline in serum concentrations of IL-4 ($p = 0.001$), IL-6 ($p = 0.006$), and hsCRP ($p = 0.004$) while TNF-α and TNF-β and mean ESR remained unchanged by the end of the trial ($p > 0.05$) in the curcumin group;[12] secondary analysis revealed improvements in antioxidant status (superoxide dismutase and reduced glutathione) and reduced lipid peroxidation (malondialdehyde)[74]	5 mg bioperine included in capsules to enhance oral bioavailability of curcuminoids Limitations of this study include a small sample size, short duration of study and follow-up, testing only a single dose of curcuminoids, and limiting inclusion of patients with mild to moderate OA
Low-dose curcumin in knee OA: A randomized, open-label, active-control clinical trial[75]	84 enrolled, 72 completed, 35 in curcumin-galactomannoside (CGM) group and 37 in active-control group	400 mg low-dose CGM compared with 500 mg glucosamine hydrochloride and 415 mg chondroitin sulfate as a single oral dose twice daily for 6 weeks	CGM led to improvement in VAS and walking performance as well as in stiffness, physical function, and total WOMAC scores *versus* active-control group ($p < 0.001$)	CGM reduced serum inflammatory markers (hsCRP, IL-1, IL-6, IL-1β, and sVCAM) *versus* active-control group ($p = 0.001$)	Limitations of this study include lack of substantive correlation between WOMAC data with symptoms and subjective nature of clinical measurements
Double-blind, randomized controlled study of CGM/glucosamine combination[76]	80 patients with OA randomized 1:1 to equal groups	400 mg CGM with 500 mg glucosamine hydrochloride (GLN) OR 415 mg chondroitin sulfate (CHN) with 500 mg GLN taken as a single oral dose twice a day for 84 days	CGM-GLN improved walking performance, VAS score, KPS score, and WOMAC total score *versus* CHN-GLN ($p < 0.001$)	CGM-GLN reduced inflammatory serum markers (IL-1β, IL-6, and sVCAM) more than CHN-GLN	NA
Double-blind, randomized, placebo-controlled clinical trial of curcumin in patients with OA[77]	30 patients with OA randomized 1:1 into two groups	80 mg curcumin (with nanomicelles to improve oral absorption) or placebo once daily for 3 months; option for 50 mg diclofenac sodium for analgesic	VAS score significantly decreased in curcumin group *versus* placebo ($p < 0.0001$)	Significant CRP decrease ($p = 0.01$) in curcumin group *versus* placebo and decrease in proportion of T cells (CD4+, CD8+, Th17) ($p < 0.01$)	Curcumin was encapsulated in nanomicelles to improve its oral absorption All patients received 50 mg of diclofenac sodium on a routine basis and for ethical reasons Limitations of this study include a small sample size and short duration of follow-up

(Continued)

Table 1. (Continued)

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
Comparison of *Curcuma domestica* extract with ibuprofen in patients with knee OA[78]	367 patients, 185 in the curcumin group and 182 in the ibuprofen group	*Curcumin domestica* 1500 mg/day or ibuprofen 1200 mg/day for 4 weeks	*Curcumin domestica* was non-inferior to ibuprofen in the WOMAC total, WOMAC pain, and WOMAC function scores	Not reported	Number of abdominal pain/discomfort adverse events were higher in the ibuprofen group *versus* the curcumin group ($p = 0.046$) Limitations of this study include a small sample size, subtherapeutic dose of ibuprofen (800 mg/day), single-blinded assessor, and unequal frequency of drug intake between study groups
Randomized, double-blind, controlled clinical trial of herbal formulation *versus* naproxen in patients with chronic knee OA[79]	60 patients randomly assigned 1:1 to herbal formulation or naproxen	Herbal formulation (300 mg curcumin, 7.5 mg gingerols, 3.75 mg piperine) twice daily after meals or 250 mg naproxen twice in the morning and night for 4 weeks	Not reported	PGE_2 decreased significantly in both groups ($p < 0.001$), but there were no significant differences between groups	Inflammation suppression observed with herbal mixture was similar to naproxen, suggesting benefits for long-term treatment Limitations of this study include the assessment of only one inflammatory marker, not measuring the anti-inflammatory effects of each herb separately, and heterogeneous diet of the study population
Randomized clinical trial for nanocurcumin for knee OA[25]	36 patients in the nanocurcumin group and 35 patients in the placebo group	40 mg of nanocurcumin every 12 h for 6 weeks	Significant decrease ($p < 0.001$) observed in overall score and scores of pain, stiffness, and physical activity subscales of WOMAC in nanocurcumin group *versus* placebo	Not reported	Larger decrease in use of acetaminophen in the second 3 weeks in the nanocurcumin group *versus* placebo; no adverse events reported Limitations of this study include a small sample size, short duration of study, and testing only a single dose of nanocurcumin
Curcumin solid lipid particles for treatment of knee OA[80]	50 patients recruited, 42 completed; 25 in ibuprofen group and 17 in curcumin group	400 mg of solid lipid curcumin particles (80 mg of curcumin per capsule) twice daily or 400 mg ibuprofen once daily with placebo for 90 days	Significant improvements in VAS and WOMAC scores were observed from baseline in the curcumin group, similar to ibuprofen group, but no differences between groups were observed	No difference between groups in inflammatory markers	A limitation of this study was the low dose of curcumin and ibuprofen

(Continued)

Table 1. (Continued)

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
Curcumin versus diclofenac treatment in knee OA in a randomized, open-label, parallel-arm study[81]	149 patients randomly assigned 1:1 to one of two treatment groups	500 mg curcumin three times daily or 50 mg diclofenac tablet twice daily for 28 days	Similar improvement in severity of pain and KOOS scale in curcumin group *versus* diclofenac; no statistically significant difference	Not reported	Fewer adverse events in curcumin group *versus* diclofenac group ($p < 0.01$) Limitations of this study include the lack of a placebo-controlled group, short duration of study, and the use of subjective measures of pain
Randomized, double-blind, placebo-controlled study of glucosamine hydrochloride, chondroitin sulfate, and biocurcumin with exercise in patients with knee OA[82]	53 patients randomly assigned to treatment ($n = 26$) or placebo ($n = 27$)	Both groups received 20 sessions of physical therapy; two tablets of a dietary supplement (chondroitin sulfate, glucosamine hydrochloride, and Bio-Curcumin BCM-95®, a highly bioavailable *Curcuma longa* extract titrated to 95% from curcuminoids) or placebo were taken each day for 8 weeks	Compared with controls, the treatment group showed reductions in VAS scores at motion at 8 weeks ($p = 0.045$) and in Lequesne index ($p = 0.009$)	No changes observed in inflammatory markers	Limitations of this study include the short duration of follow-up and no further radiographic assessment beyond X-ray examination
Open-label study of curcumin and glucosamine *versus* chondroitin and glucosamine[26]	124 patients; 63 in the curcumin + glucosamine group and 61 in the chondroitin + glucosamine group	Tablet: curcumin supplement 500 mg [mg amount of curcumin not reported; mfr reports 15% (75% of 20% total curcuminoids)] + glucosamine 500 mg Capsule: chondroitin 400 mg + glucosamine 415 mg	Curcumin combination achieved higher scores *versus* baseline and chondroitin on KPSI and WOMAC ($p < 0.05$ for all); walking distance on a treadmill was longer at 1 month to end of study with curcumin *versus* chondroitin ($p < 0.05$); decrease in rescue medication, curcumin *versus* chondroitin ($p < 0.05$)	Not reported	Limitations of this study include a small sample size, short duration of follow-up, and lack of randomization

(Continued)

Table 1. (Continued)

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
Investigation of short-term effects of curcumin and exercise in knee OA[83]	25 patients; 13 in the curcumin group and 12 in the curcumin with exercise group	700 mg capsule three times daily for 4 weeks (total 2100 mg, 35 mg/kg bodyweight) All patients were given a step-measuring instrument to record daily steps in addition to exercise time	Improvements in VAS ($p < 0.001$), WOMAC score for pain ($p < 0.001$), physical function difficulties ($p < 0.01$), and total score ($p < 0.01$) were observed with each treatment after 4 weeks, but no differences were detected between groups	Not reported	A limitation of this study was the short duration of treatment
Randomized, double-blind, placebo-controlled study of highly bioavailable curcumin for knee OA[84]	50 patients randomized 1:1 to treatment or placebo; final analysis of 18 in the curcumin group and 23 in the placebo group	Highly bioavailable curcumin 180 mg per day for 8 weeks or placebo (capsules of similar shape and size with starch, dextrin, and maltose)	VAS scores were significantly lower in the curcumin group *versus* placebo ($p = 0.023$), except in patients with initial VAS scores of $\leqslant 15$	Not reported	Celecoxib dependence was significantly lower at 8 weeks in the curcumin group *versus* placebo ($p = 0.0252$) Limitations of this study include a small sample size and short duration of treatment
Double-blind, multicenter, randomized, placebo-controlled, three-arm study with bio-optimized *Curcuma longa* (BCL) extract in knee OA[85]	150 patients with knee osteoarthritis randomized 1:1:1	High-dose BCL: three capsules two times daily; low-dose BCL: two capsules two times daily (each capsule contained 46.67 mg of turmeric rhizome extract); or placebo (capsules contained sunflower seed oil) for 90 days	VAS knee pain was significantly reduced in both BCL groups *versus* placebo ($p = 0.018$) and both curcumin groups showed a greater decrease of PGADA than placebo; KOOS decreased over time for all treatment arms, but no differences were observed across treatment groups	sColl2-1, a biomarker identified in an earlier study[86] of 22 patients with knee OA under the high-dose BCL treatment regimen was decreased in all groups between times 1 and 3; when high and low doses were pooled, there was a significant difference between the pooled BCL groups and placebo ($p = 0.031$) between baseline and time 3 in the larger study (i.e. 150 patients)	Number of adverse events linked to high-dose BCL group *versus* low-dose BCL and placebo ($p = 0.012$) Limitations of this study include a small sample size and limiting the study population to nonresponders of standard OA pain treatment

(Continued)

Table 1. (Continued)

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
Randomized controlled trial of *Curcuma longa* extract as adjuvant therapy to diclofenac for knee OA[87]	44 patients randomized to each treatment group	Diclofenac 75 mg per day with placebo or diclofenac 75 mg per day with curcumin 1000 mg per day for 3 months	No difference observed in VAS score improvement between groups and no statistical difference in KOOS, but curcumin group had better scores in pain and function in daily living	Not reported	Limitations of this study include drop out cases and low dose of curcumin
Curcumin in asymptomatic subjects with low bone density[88]	57 patients; 28 in the control group and 29 in the supplement group	1000 mg of curcuminoids [mg amount of curcumin not reported; mfr reports 15% (75% of 20% total curcuminoids)] Standard management: nutritional evaluation, supplying a diet with adequate vitamins D and C and calcium; regular exercise program of 20 min at least four times per week (e.g. light weightlifting and walking or running)	Heel bone, small finger bone, and upper jawbone density significantly improved *versus* baseline by 12 weeks ($p < 0.05$) with continued improvement at 24 weeks with curcumin ($p < 0.05$); no significant improvements from baseline with standard management alone	Not reported	Curcumin could improve several aspects of bone health Limitations of this study include a small sample size and inclusion of only an asymptomatic population
Long-term evaluation of curcumin tablets[10]	100 patients with knee OA diagnosed by X-ray	Two 500 mg tablets daily (~200 mg curcumin); curcuminoid mixture was 75% curcumin, 15% demethoxycurcumin, and 10% bisdemethoxycurcumin Control group: best available treatment	WOMAC pain score was reduced from 16.6 to 7.3 ($p < 0.05$) and WOMAC stiffness score was reduced from 7.4 to 3.2 ($p < 0.05$); no significant change in control group for either score	IL-1β, IL-6, soluble CD40 ligand, sVCAM-1, and ESR were all significantly reduced ($p < 0.05$) *versus* control after 8 months of treatment	NSAIDs/other pain killer use decreased significantly in the treatment group ($p < 0.05$) *versus* baseline Limitations of this study include a small sample size and short duration of treatment

ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; KOOS, knee injury and osteoarthritis score outcome; LPFI, Lequesne pain functional index; KPS, Karnofsky performance scale; KPSI, Karnofsky performance scale index; mfr, manufacturer; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGADA, patient global assessment of disease activity; PGE_2, prostaglandin E_2; sVCAM-1, soluble vascular cell adhesion molecule; TNF, tumor necrosis factor; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities score.

that curcumin is effective at reducing musculoskeletal pain and inflammation in patients with OA, thereby increasing function and quality of life.

A meta-analysis of five studies with 599 patients with OA concluded that curcumin improved the Western Ontario and McMaster Universities (WOMAC) score and visual analog scale (VAS) score compared with placebo (both $p < 0.01$).[89] There was no statistical difference between curcumin and placebo for side effect rate nor was there a difference between curcumin and ibuprofen.[89] Another systematic review and meta-analysis focused on 32 randomized controlled trials ($N = 2038$ participants) that evaluated the anti-inflammatory effects of oral curcumin through blood concentrations of inflammatory markers.[90] Large reductions in TNF-α, MCP-1, IL-8, IL-6, and C-reactive protein (CRP) concentrations were observed in participants treated with curcumin versus those in the control group (all $p < 0.01$), further supporting *in vitro* and preclinical model findings.[90]

Furthermore, a systematic review and meta-analysis of 11 randomized controlled trials comparing the efficacy of turmeric extracts *versus* placebo and five trials comparing efficacy *versus* NSAIDs in 1810 adults with knee OA showed turmeric significantly reduced knee pain and improved physical function compared with placebo but had effects similar to NSAIDs.[91] Although biomarkers of inflammation were evaluated in multiple trials, there were no significant between-group differences reported.[91] Rates of adverse events were lower in the turmeric extract groups *versus* those for NSAIDs; however, rates were similar between groups treated with turmeric extract and placebo.[91] An additional study suggests that long-term use of curcumin supplements for the management of OA is preferred to improve pain and reduce stiffness.[92] Therefore, curcumin at doses between 160 and 2000 mg/day was efficacious in the management of OA and demonstrated similar efficacy to NSAIDs, including diclofenac (100 mg day) and ibuprofen (400–1200 mg/day).[80,81,89,91]

Combining curcumin with other natural ingredient supplements for management of OA pain has also been investigated in clinical trials. Notably, two clinical trials showed significant benefit from the combination of curcumin and glucosamine as measured by improvement in walking ($p < 0.001$) and pain (reduced VAS score; $p < 0.05$ for both studies compared with control group), suggesting that combining curcumin with other natural product supplements may be beneficial in OA.[76,82]

Boswellic acids for OA

Clinical trials of boswellic acids in OA suggest that formulation and composition of the oral capsules/tablets influences efficacy in reducing pain and increasing function (Table 2).[11,93–95] The majority of clinical trials had a smaller number of participants, but two randomized trials had more than 100 participants ($N = 120$ and $N = 440$) and showed that boswellic acids demonstrated equal effectiveness in the management of OA pain compared with glucosamine.[13,96] In the smaller of these two prospective randomized trials, patients with knee OA ($N = 120$) received either boswellic acids or glucosamine sulfate for 60 days. VAS and Lequesne total scores were assessed during follow-up visits at 2 and 6 months.[13] At baseline and 2 months, patients treated with boswellic acids had higher mean VAS and Lequesne total scores *versus* patients treated with glucosamine; however, these scores were lower at 6 months with boswellic acids *versus* glucosamine treatment ($p = 0.08$ and $p = 0.02$, respectively). Patients treated with glucosamine showed early reduction of mean scores at 2 months, but scores remained generally unchanged from 2 to 6 months.[13] Biomarkers of inflammatory pathways were not reported in the clinical trials evaluating boswellic acids for OA pain management; therefore, further research is needed to confirm *in vitro* and preclinical model findings. Boswellic acids have a well-defined safety profile with few adverse events reported during clinical trials.

Combination of curcumin and boswellic acids

Several studies have investigated the combination of curcumin and boswellic acids as management for OA pain (Table 3). One primary study ($N = 201$) showed that the combination of curcumin and boswellic acids reduced WOMAC total score ($p < 0.001$) from baseline to visit 3 at 84 days and compared with placebo ($p < 0.05$)

Table 2. Clinical trials of boswellic acids for OA.

Study	Number of participants	Treatment regimen	Efficacy	Biochemical outcomes	Notes
Randomized, double-blind, placebo-controlled trial to assess *Boswellia serrata* extract (BSE) for treatment of knee OA[93]	48 patients randomized 1:1 to BSE or placebo	Two tablets of 169.33 mg BSE with AKBA and 87.3 mg of total BBA or placebo for 120 days	BSE significantly improved physical function through pain and stiffness reduction (WOMAC score) *versus* placebo and baseline ($p < 0.001$)	BSE significantly reduced hsCRP ($p < 0.01$) *versus* placebo	Radiographic assessment showed improvement in knee joint gap and reduced spurs, confirming BSE efficacy Limitations of this study include a small sample size and the use of only one potential inflammatory marker (hsCRP) associated with knee OA
Double-blind, randomized, placebo-controlled clinical study evaluating efficacy of boswellic acids in patients with knee OA[94]	60 patients; 30 in the treatment group and 30 in the placebo group	50– mg capsule containing at least 20% AKBA or placebo twice daily for 30 days	Improved pain scores and physical function scores *versus* placebo (VAS, LPFI, WOMAC pain, WOMAC function, $p < 0.0001$; WOMAC stiffness, $p = 0.0014$); improvements with boswellic acids were observed as early as day 5 (VAS, LPFI; $p < 0.05$ each)	Not reported	No major adverse events reported A limitation of this study is the short duration of treatment
Randomized, double-blind controlled clinical trial comparing natural ingredients with ibuprofen in patients with knee OA[97]	75 patients randomly assigned to three groups: 23 to Elaeagnus, 26 to Elaeagnus/ Boswellia, and 26 to ibuprofen	Elaeagnus (200 mg), Elaeagnus/ *Boswellia thurifera* (100 mg/100 mg with 60–70% boswellic acids and 3% 11-ketoboswellic acid), or 400 mg ibuprofen three times daily for 4 weeks	Significant reductions in VAS, LPFI, and PGA scores across groups ($p < 0.001$), but no difference between groups	Not reported	GI side effects reported for all three groups A limitation of this study is the short duration of treatment
Randomized trial comparing hyaluronic acid intra-articular injections with *Boswellia serrata*[98]	60 patients with knee OA; 30 in each group	Group A: 3 weekly intra-articular injections with hyaluronic acid 1.6%; Group B: oral hyaluronic acid 300 mg with 100 mg *Boswellia serrata* extract for 20 days and hyaluronic acid 150 mg for 20 days	Improvement in AKSS and VAS score in both groups; age difference observed with younger patients having greater reductions in Group A and older patients having greater reductions in Group B	Not reported	Combined therapy might be beneficial depending on the age of the patient for treatment of early OA
Double-blind, controlled equivalence trial between Boswellia with other herbal extracts, glucosamine sulfate, and celecoxib[96]	440 patients with knee OA randomized 1:1:1:1	Group 1: 400-mg capsule containing *Tinospora cordifolia*, *Zingiber officinale*, *Emblica officinalis*, and *Boswellia serrata*; Group 2: same as Group 1 except *Boswellia serrata* was not included; Group 3: glucosamine sulfate 2 g daily; Group 4: 200 mg daily; all doses for 24 weeks	Knee pain was reduced and knee function improved across groups and was equivalent to the other treatment groups	Not reported	Rise in serum glutamic pyruvic transaminase in 26 patients from Group 1; levels normalized 8–12 weeks after stopping treatment Limitations of this study include a high patient withdrawal rate (29%), an epidemic of chikungunya and/or dengue in 2006 which was associated with acute severe musculoskeletal pains, and lack of a whole system/pragmatic treatment approach

(Continued)

Table 2. (Continued)

Study	Number of participants	Treatment regimen	Efficacy	Biochemical outcomes	Notes
Prospective randomized clinical trial to assess methylsulfonylmethane and boswellic acids for the treatment of knee OA[27]	60 patients randomized 1:1 to experimental or control group	Experimental: 5 grams of methylsulfonylmethane and 7.2 mg of boswellic acids Control: placebo Daily for 60 days	No difference in VAS score or LI at 2 or 6-month follow-up	Not reported	Statistically significant difference in patients need for anti-inflammatory drugs, lower in experimental than control ($p < 0.0001$) Limitations include lack of a control group and imaging tests, small study population, and restriction of inclusion criteria to patients with low LI (> 2)
Randomized trial comparing methylsulfonylmethane and boswellic acids *versus* glucosamine sulfate for knee OA[13]	120 patients randomized 1:1 to experimental or control group	Experimental: 5 g of methylsulfonylmethane and 7.2 mg of boswellic acids; Control: 1500 mg of glucosamine sulfate for 60 days	VAS and Lequesne index total scores were significantly reduced in both groups, with better mean value at 6 months/end of the study in experimental group	Not reported	Reduction in the need of anti-inflammatory drugs was observed for both treatment arms Limitations include lack of diagnostic imaging as well as blinded administration of the two integrators
Double-blind, randomized, placebo-controlled study of boswellic acids for treatment of knee OA[95]	75 patients randomized 1:1:1 to 100 or 250 mg boswellic acids or placebo	50 mg boswellic acids with 30% AKBA or 125 mg boswellic acids with 30% AKBA twice daily for 90 days	Both groups (100 and 250 mg) significantly improved pain and physical ability scores *versus* baseline ($p < 0.0001$ each dose, all measures, at 90 days); VAS decreased significantly from baseline by day 7 with both doses (100 mg, $p = 0.05$; 250 mg, $p = 0.02$) *versus* placebo; high-dose group showed significant increase in WOMAC physical function by day 7 ($p < 0.01$) *versus* placebo	Not reported	NA
Randomized, double-blind, placebo-controlled clinical study comparing two boswellic acid formulations in knee OA[11]	60 patients randomized 1:1:1 to Formulation 1 or 2 or placebo	Formulation 1: 50 mg containing at least 20% AKBA; Formulation 2: 50 mg containing at least 30% AKBA; both twice daily for 90 days	Both improved pain and physical function scores *versus* baseline ($p < 0.0001$, Formulation 1 on all measures at 90 days; $p < 0.0001$, Formulation 2 on all but WOMAC stiffness ($p = 0.0001$] at 90 days); improvement with both as early as 7 days (Formulation 1, $p < 0.05$ for LPFI, WOMAC pain, stiffness, function, $p < 0.0005$ for VAS; Formulation 2, $p < 0.05$ for VAS, WOMAC function); Formulation 1 > Formulation 2 on all tested pain scores, and was considered superior to Formulation 2	Not reported	NA
Randomized, double-blind, placebo-controlled trial of *Boswellia serrata* extract (BSE) for knee OA[99]	30 patients with knee OA; 15 received placebo, 15 received BSE	333 mg of BSE per capsule taken three times daily for 8 weeks (40% boswellic acids with KBA at 6.44% and AKBA at 2%)	BSE decreased knee pain and frequency of swelling, increased knee flexion, and increased walking distance with BSE *versus* placebo ($p < 0.001$)	Not reported	No radiologic changes; GI-related adverse events, none led to discontinuation A limitation of this study was the small sample size

AKSS, American Knee Society Score; BBA, β-boswellic acid; GI, gastrointestinal; hsCRP, high-sensitivity C-reactive protein; LPFI, Lequesne pain functional index; NA, not applicable; OA, osteoarthritis; PGA, patient global assessment; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities score.

Table 3. Studies of curcumin and boswellic acids in combination for OA pain.

Study	Number of participants	Treatment regimen	Clinical outcomes	Biochemical outcomes	Notes
OA – general population					
Comparative, randomized, double-blind, placebo-controlled phase II study of curcumin and its combination with boswellic acids in OA[24]	201 patients; 67 boswellic acids + curcumin, 66 curcumin-alone, 68 placebo	500 mg three times daily of curcumin alone, curcumin with boswellic acids [350 mg curcumin extract ~65% + boswellia extract 150 mg (75% boswellic acids, 10% AKBA)] or placebo for 12 weeks	WOMAC OA total index and joint pain index decreased significantly after 12 weeks of continuous treatment with curcumin *versus* placebo ($p < 0.05$); combination was better than curcumin alone for physical performance tests	Not reported	NA
Two-arm clinical trial of boswellic acids + curcumin *versus* celecoxib in knee OA[100]	30 patients; 15 boswellic acids + curcumin, 15 celecoxib (100 mg) group	500 mg BID; curcumin extract 350 mg (70% curcumin, 17% demethoxycurcumin, 3.5% bisdemethoxycurcumin) + boswellia extract 150 mg (75% boswellic acids and 10% AKBA)	Significant improvements from baseline in physician-evaluated pain scores, walking distance, and joint line tenderness in both groups	Not reported	NA
RADIANT Study: Internet-based, parallel, randomized, double-blind, placebo-controlled trial of supplement combination in hand OA[101]	106 patients over 40 years old with hand OA randomized 1:1	BSE 250 mg/day, PBE 100 mg/day, MSM 1500 mg/day, and curcumin 168 mg/day for 12 weeks (7 capsules per day divided into two doses taken with food)	No significant difference between supplement combination and placebo in pain VAS or secondary outcomes for function/impairment	Not reported	Limitations of this study include that it was conducted online, which may have led to errors and affected the results as technology literacy and skill was required to complete the online surveys; there may have been a spontaneous bias to report high adherence as treatment adherence was mainly determined by participant self-reported capsule counting; patients with early OA were not correctly identified prior to randomization and were therefore not balanced in the 2 study groups; and data from this study may have been impacted by the physical and emotional impact of COVID-19 and the Australian bushfires
Placebo-controlled, double-blind study of combined *Terminalia chebula* fruit, curcumin, and boswellia extracts in patients with knee OA[102]	105 patients randomized to three groups ($n = 35$ each)	Group 1: 200 mg per day of extract combination (*Terminalia chebula* fruit, alcohol extract of *Curcuma longa* rhizome, and *Boswellia serrata* extract at 2:1:2 ratio); Group 2: 400 mg per day of extract combination; Group 3: placebo; all for 90 days	Improved physical function (WOMAC pain, stiffness, physical function) and quality of life (LPFI), decreased pain (VAS score) in both extract groups *versus* placebo ($p < 0.001$)	Not reported	No significant safety issues, minor adverse events across all three groups
Double-blind, placebo-controlled, crossover study of an herbomineral formulation in OA[23]	42 patients with OA randomized 1:1	Two capsules of herbomineral formulation every 8 h after food: roots of *Withania somnifera*, stem of *Boswellia serrata*, rhizomes of *Curcuma longa*, and a zinc complex (Articulin-F) for 3 months	Herbomineral formulation led to significant decrease in pain severity ($p < 0.001$) and disability score ($p < 0.05$)	Not reported	Limitations of this study include a small sample size and short duration of treatment

BID, twice daily; LPFI, Lequesne Pain Functional Index; MSM, methylsulfonylmethane; NA, not applicable; OA, osteoarthritis; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities score.

after 3 months of continuous treatment.[24] The treatments were well tolerated and no serious adverse events were observed.[24] Because there are a limited number of clinical studies, additional studies are needed to fully understand the potential synergy of curcumin and boswellic acids for the management of OA pain. Investigation of curcumin and boswellic acids alone and in combination allows for the identification of synergistic pharmacologic effects.[22] The synergistic activity of these two natural ingredients could reduce the dosage and frequency of consumption of acetaminophen and NSAIDs, as both individually have been shown to reduce NSAID use, which would be advantageous for patients with OA through decreased NSAID exposure and associated adverse events.[10,12,13,25–27] A 2-by-2 factorial randomized controlled trial is needed to provide evidence for the synergistic effects.

In addition to the number of clinical trials evaluating the combination, further support comes from numerous animal studies that evaluated the combination of curcumin and boswellic acids in other disease states, including rheumatoid arthritis and cancer. Preclinical data on the combination of solubilized micellar curcumin and micellar *Boswellia* in the treatment of rheumatoid arthritis in a rat model showed anti-inflammatory effects comparable to NSAIDs even at much lower doses.[103] In addition, preclinical data suggest a possible role for the combination of curcumin and boswellic acids as chemoprevention of colorectal cancer and as an antiviral agent.[104–106] Antiproliferative and proapoptotic effects were observed simultaneously, as well as the promotion of epithelial turnover in the adenomatous polyposis coli (Apc) mouse model for intestinal carcinogenesis in animals receiving an enriched diet with curcumin, AKBA, and silymarin for 110 days.[105] Although the animals with the enriched diet still developed small bowel carcinomas at a similar rate to those animals receiving the standard diet (85% *versus* 100%), the enriched diet led to a significant ($p < 0.001$) decrease in the number and size of polypoid lesions.[105] In further support of the chemopreventive effects of curcumin and AKBA, a mouse xenograft model demonstrated that each product alone suppressed tumor growth, but when used in combination, synergistic tumor suppression was observed.[104]

Curcumin and boswellic acids (as well as other constituents, such as maritime pine) were studied in combination for other indications in clinical trials in humans, including acute musculoskeletal pain, chronic kidney disease, benign thyroid nodules, diverticulitis, tendinopathy, and Gulf War syndrome.[107–112] In healthy adults with acute musculoskeletal pain, treatment with the combination of curcumin and boswellic acids or with acetaminophen for 7 days reduced pain intensity at a similar rate and to a similar level.[113] The only difference observed between the two groups was improved reduction in the affective domain of the McGill Pain Questionnaire in the curcumin and boswellic acids treatment group (8.57 times better, $p = 0.027$).[113] In patients with early-stage chronic kidney disease, treatment with curcumin and boswellic acids for 8 weeks increased PGE_2 levels to a lesser extent than placebo.[109] Spirulina–curcumin–boswellia (400–50–50 mg per capsule, twice daily for 6 weeks) was effective in reducing the size of benign thyroid nodules in 29 of 34 patients; although the authors of the study did not specify a mechanism, they did propose that this reduction may be related to the anti-inflammatory effects of the natural ingredients.[108] An investigation in healthy adult males who were master athletes that followed the Mediterranean diet and took a curcumin and Boswellia serrata supplement for 3 months showed significant decreases in advanced glycation end products and malondialdehyde compared with those who only followed the Mediterranean diet ($p < 0.05$), suggesting that supplementation could improve muscle performance.[114]

Pharmacokinetics of boswellic acids and curcumin

A phase I, crossover study showed that there were no pharmacokinetic interactions between curcumin and boswellic acids when administered in combination, and no adverse events were reported when either supplement was taken alone or in combination.[21]

Safety

Both curcumin and boswellic acids ingredients have been 'generally recognized as safe' by the World Health Organization,[115,116] and there is a long history of their use. However, for both curcumin and boswellic acids, some allergic dermatitis was reported for individuals who frequently handle the natural product.[115,116] Overall, curcumin and boswellic acids in combination are associated with few/infrequent adverse events.

Limitations

The conclusions of this review are based on our review of the literature and should be interpreted with caution as we did not perform an independent critical appraisal of selected trials. This was beyond the scope of this manuscript as this is a narrative literature review and not a systematic literature review. Another limitation is that no definitive conclusion could be made regarding the synergism of using curcumin and boswellic acids together for the management of inflammation and pain in OA. While a few studies have compared the effects of the combination of curcumin and boswellic acids, these studies have compared the effects of the combination treatment with placebo and not with each treatment individually. Therefore, additional studies are required to conclusively demonstrate the synergistic effect of these treatments.

Conclusion

This review article integrates all available data on curcumin and boswellic acids for the management of inflammation and pain in OA and provides the rationale for the combined use of these ingredients. Further metabolomic studies to determine if microbial metabolites of curcumin and boswellic acids are related to their clinical efficacy would be helpful for dosing recommendations. Additional research on absorption, as well as determination of bioavailability and the relationship with clinical efficacy is needed for curcumin to establish a dose-effect.[22] There may also be potential in using concentrated extracts of curcumin and boswellic acids to overcome issues with bioavailability.[54,59] The anti-inflammatory effects of boswellic acids and curcumin have translated to the improvement of symptoms of OA and joint pain as shown in numerous clinical trials. Antinociceptive effects were demonstrated in preclinical models of OA for both boswellic acids and curcumin. The combination of these two anti-inflammatory natural ingredients suggests potential synergistic activity, which supports their use to further improve OA symptoms and pain. This combination could also improve patients' quality of life and reduce the dosage and frequency of consumption of acetaminophen and NSAIDs.[10,12,13,25–27] Other potential mechanisms have been recognized in recent years (eg, antioxidant effects and effects on microbiota) and there are key molecular targets identified from research on cancer that are relevant to OA (i.e. PI3K or AKT enzymes).[22] There is support for the use of curcumin and boswellic acids in combination to reduce inflammation and pain in patients with OA.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Vidhu Sethi: Formal analysis; Writing – original draft; Writing – review & editing.

Manohar Garg: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Maxime Herve: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Ali Mobasheri: Conceptualization; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

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Manohar Garg has no relevant disclosures to report.

Vidhu Sethi is an employee of Haleon.

Maxime Herve was an employee of GlaxoSmithKline Consumer Healthcare at the time this article was prepared and is now an employee of Sanofi.

Ali Mobasheri is President of the Osteoarthritis Research Society International and has served as a member of the GlaxoSmithKline Naturals Advisory Board. He has no further disclosures to report.

Availability of data and materials

All references cited in this manuscript are available to the public.

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