

## REVIEW ARTICLE

# EFFICACY OF HERBAL AND NATURALLY-DERIVED DIETARY SUPPLEMENTS FOR THE MANAGEMENT OF KNEE OSTEOARTHRITIS: A MINI-REVIEW

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## ABSTRACT

Knee osteoarthritis (OA) accounts for approximately 85% of the burden of OA worldwide. Knee OA is a whole joint disorder involving structural alterations in the hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles. The complex knee OA pathogenesis includes mechanical, inflammatory, and metabolic factors, eventually leading to the synovial joint's structural destruction and failure. This review aims to present an overview of current knowledge on dietary supplements, such as glucosamine, chondroitin, methylsulfonylmethane, diacerein, avocado-soybean unsaponifiables, curcuminoids, as well as boswellic acids. Results originating from several small studies with natural products in managing knee OA are encouraging. However, additional well-designed placebo-controlled clinical trials are required.

**KEY WORDS:** curcuminoids, osteoarthritis, boswellic acids, ginger, complementary and alternative medicines, CAM

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## INTRODUCTION

Osteoarthritis (OA) is a common and disabling disorder representing a substantial and increasing health burden with significant implications for the individuals affected, health-care systems, and wider socioeconomic costs. Considering aging and increasing obesity, and increasing numbers of joint injuries, this already burdensome syndrome is becoming more prevalent, with worldwide estimates indicating that 250 million people are affected [1].

In clinical practice, the knee is the most frequent OA site, followed by the hand and hip. A knee OA stands for 85% of the OA burden worldwide [2]. The medical cost of OA in high-income countries was estimated to account for 1% – 2.5% of the gross domestic product, with hip and knee joint replacements representing a significant proportion of these health-care costs [3]. In the case of knee OA, substantial evidence indicates several moderate to strong risk factors, such as female sex, obesity, and previous knee injury [4]. Knee malalignment is also a moderate to strong risk factor, and knee extensor muscle weakness is likely to be a weak risk factor [5, 6].

Currently, treatment of OA comprises lifestyle changes (e.g., weight reduction with exercise and diet), physical aids (e.g., canes or braces), physical therapies, and medications including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and/or complementary and alternative medicines (CAMs) [7].

A couple of years ago, Liu et al. prepared a meta-analysis assessing various CAMs [8]. Authors evaluated twenty

CAMs in 69 studies. They demonstrated that *Curcuma longa* extract, *Boswellia serrata* extract, collagen hydrolysate, passion fruit peel extract, pycnogenol, and L-carnitine exerted an evident beneficial impact on pain decrease. A smaller impact was observed in the case of avocado soybean unsaponifiables, chondroitin, diacerein, glucosamine, undenatured type II collagen, and methylsulfonylmethane.

## THE AIM

This review aims to present an update on current knowledge of the most commonly used and newly available dietary supplements in knee OA management.

## REVIEW AND DISCUSSION

### PATHOPHYSIOLOGY OF OSTEOARTHRITIS

Osteoarthritis is a whole joint disorder involving structural alterations in the hyaline articular cartilage, subchondral bone, ligaments, capsule, synovium, and periarticular muscles. The complex OA pathogenesis includes mechanical, inflammatory, and metabolic factors, eventually leading to structural destruction and failure of the synovial joint [9, 10].

Osteoclasts originate from hematopoietic cells that also give the beginning for macrophages and monocytes. The Receptor Activator NF- $\kappa$ B Ligand (RANKL) is synthe-

sized by chondrocytes, osteoblasts, and stromal. After RANK activation due to binding to RANKL in the osteoclast precursor cells' membrane, these cells differentiate into osteoclasts [11]. To hamper osteoclasts' activation, osteoprotegerin (OPG), also synthesized in osteoblasts, plays a decoy receptor's role and prevents binding of RANKL to RANK. In consequence, the osteoclastogenesis process is not initiated. The OPG also plays a role in triggering apoptosis of mature osteoclasts. Thus, the RANKL/OPG ratio is an excellent index to analyze the occurrence of osteogenesis or osteoclastogenesis. When RANKL/OPG ratio increases, bone destruction dominates, and when this index decreases, subchondral bones are more protected. In OA, various interleukins and cytokines such as IL-1 $\beta$ , IL-6, IL-11, IL-17, and TNF- $\alpha$  predispose to increased RANKL formation as well as decreased OPG synthesis, leading to bone loss [12].

Additionally, several other proteases are involved in OA, such as matrix metalloproteinases 3, 9, and 13 (MMP-3, MMP-9, MMP-13), tartrate-resistant acid phosphatase (TRAP), or metalloproteinase with thrombospondin Motifs (ADAMTS). IL-1 acts on chondrocytes, resulting in the induction of NF- $\kappa$ B and activator protein 1 (AP-1) and the production of MMPs, enzymes that breakdown collagen. Among the metalloproteinase, MMP-13 is more potent in the cleavage of type II collagen. The ADAMTS acts in cleaving aggrecan molecules (another component of cartilage). In OA, these proteases are increased, leading to abnormal destruction of cartilage. IL-6 also plays a significant role in chondrocytes by diminishing type II collagen synthesis. Probably, TNF- $\alpha$  works in synergy with these interleukins in the inhibition of proteoglycan synthesis and increasing cartilage resorption [13, 14].

## GLUCOSAMINE/CHONDROITIN

Glucosamine is predominantly found at the level of connective tissue and cartilage. At the articular level, it is an essential precursor for glycosaminoglycan in the production of hyaluronic acid, keratan sulfate, chondroitin sulfate, aggrecan, and collagen type II, which are vital components of the cartilage matrix. Glucosamine inhibits the synthesis of the vital cleavage enzymes in the cartilage, MMP, resulting in a decreased proteoglycan degradation. Additionally, glucosamine hampers proinflammatory processes. Jerosch et al. proved that glucosamine (1.5 g per day) significantly decreased the total knee replacement rate in subjects with knee OA (from 14.5 to 6.3%) and ceased the joint space loss progression [15]. Other studies also confirmed the glucosamine's chondroprotective properties [16]. These properties are believed to be associated with diminished chondrocyte apoptosis, a decrease in MMP-3 levels, and an increase in TGF- $\beta$ 1 and connective tissue growth factor (CTGF) levels [17]. Unfortunately, Kwoch et al. disclosed no structural improvements in MRI knee appearance and CTX-II urinary excretion in subjects using glucosamine in a dose of 1.5 g per day for 24 weeks [18].

Chondroitin sulfate is an essential component of the extracellular matrix, being the most frequent glycosaminoglycan in the aggrecan molecule within the cartilage. Several clinical studies proved the clinically significant structure-modifying impact in subjects treated with chondroitin (0.8 – 1.2 g per day). Two meta-analyses showed the importance of chondroitin in delaying the progression of knee OA [16, 19]. Chondroitin acts via several mechanisms in the cartilage. It decreases ADAMTS-4, ADAMTS-5, MMP-3, and MMP-13 levels, IL-1 $\beta$  expression as well as chondrocytes' apoptosis. Chondroitin also increases hyaluronic acid, proteoglycan, and type II collagen synthesis, as well as chondrocytes' metabolism [15]. European League Against Rheumatism (EULAR) granted chondroitin sulfate the highest level of recommendation. Consequently, chondroitin sulfate should be considered a structure-modifying drug in OA, mainly in higher doses (1.2 g per day) [20].

Also, recently Rubbio-Teres showed that due to its better tolerability profile, chondroitin/glucosamine treatment is expected to prevent thousands of adverse events over the next three years and generate considerable savings for the national health system comparing with non-steroidal anti-inflammatory drugs and cyclooxygenase 2 inhibitors [21].

## METHYLSULFONYLMETHANE

Methylsulfonylmethane (MSM) is an organosulfur compound popularly used as an anti-inflammatory agent. Several studies disclosed decreased cartilage degeneration in subjects receiving MSM. This is associated with reduced TNF- $\alpha$  expression, as well as decreased levels of IL-6, NF- $\kappa$ B, and COX-2 [22]. Previous study with knee OA subjects suggested an improvement in pain and physical function MSM supplementation (3 g twice a day) [23]. However, a recent study by Tennent et al. disclosed that MSM supplementation was not associated with any improvement in the 5 KOOS (Knee Osteoarthritis Outcome Score) subscales or the 6 POMS (Profile of Moods States) subscales at one or two months [24].

## DIACEREIN

Diacerein is an anthraquinone derivate identified in herbal remedies, e.g., yellow dock. It suppresses IL-1 $\beta$ , MMP-13, and TNF- $\alpha$ , also reducing osteoclast formation. Randomized controlled trials showed a positive effect on hip and knee osteoarthritis, but no effects were observed in hand osteoarthritis [25]. Although experts concluded a similar effect of diacerein to NSAIDs; its use is restricted in Europe and the USA due to its adverse reactions (diarrhea, hepatobiliary reactions, and skin reactions). Nevertheless, Pelletier et al. proved in a randomized clinical trial (DISSCO trial) that diacerein was non-inferior to celecoxib in decreasing knee OA pain and improving physical function. Diacerein also characterized a favorable safety profile [26].

## AVOCADO-SOYBEAN UNSAPONIFIABLES

Avocado-soybean unsaponifiables, or piascledine, are a plant-originated extracts comprising of one third avocado oil and two thirds soybean oil. It inhibits IL-1 and also stimulates the synthesis of collagen in cultures. A randomized clinical trial showed that 300 mg of piascledine administration for three years reduced the joint space narrowing changes compared to the control group [27]. Another clinical trial comparing 300 mg daily of piascledine with chondroitin sulfate for six months revealed a similar favorable effect in the case of WOMAC score, represented by a 50% decrease [28].

Simental-Mendia et al., in their meta-analysis, proved the beneficial effect of avocado-soybean unsaponifiable treatment in symptomatic knee OA but not in hip OA. Additionally, adverse events were comparable in subjects applying avocado-soybean unsaponifiable or placebo [29].

## CURCUMIN

Turmeric (*Curcuma longa*) belongs to ginger family, which grows commonly in southern and south western regions of tropical. Turmeric has been applied for ages in India and China for treating infection, dermatologic diseases, stress, and depression. Turmeric's impact on human organisms is mainly linked with an orange-yellow, lipophilic polyphenol compound, i.e., curcumin. Curcumin is obtained from the herb's rhizomes [30].

Curcumin hampers RANKL-mediated osteoclastogenesis and TNF- $\alpha$  levels. Bharti et al. proved that RANKL- and curcumin-stimulated macrophages differentiate into osteoclasts to a smaller extent than when only RANKL-stimulated [31]. Additionally, when incubated with curcumin/RANKL liposomes, these cells became smaller and characterized a diminished number of nuclei compared with macrophages incubated only with RANKL. These observations support the impacts of curcuminoids on the process of osteoclastogenesis [32].

Curcumin diminishes the proinflammatory cytokine-induced activation of NF- $\kappa$ B [31]. Moreover, TRAP and cathepsin K decreased expression promotes further osteoclastogenesis suppression [32]. Curcuminoids supplementation is associated with an increased OPG/RANKL, i.e., indicating bone development. In addition to the inhibition of osteoclastogenesis, curcumin may also inhibit pit creation [31].

Apart from postponing bone degradation, curcumin presents chondroprotective effects. It inhibits the production of MMP-1, MMP-3, MMP-9, MMP-13 [32]. Curcumin also restarts the synthesis of type II collagen and glycosaminoglycan and has an anti-apoptotic effect on chondrocytes. Another result is the inhibition of the expression of ADAMT-5. It is a vital property since aggrecanase-mediated aggrecan degradation occurs in early-stage OA [12].

Curcumin also exerts anti-inflammatory properties. In a number of studies, it was proved that curcumin might down-regulate phospholipase A2, cyclooxygenase-2, and

lipoyxygenase expression as well as decrease levels of IL-1 $\beta$ , IL-6, IL-8, PGEs, and TNF- $\alpha$ . It also acts as an inducer of apoptosis in synoviocytes, decreasing the inflammation process [33].

In 2014 a randomized, double-blind, placebo-controlled trial from Iran showed curcuminoid-receiving subjects characterized significantly lower scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Lequesne's pain functional index than subjects receiving placebo [34]. However, earlier two studies by Belcaro et al. proved the clinical efficacy and safety of Meriva, a phosphatidylcholine complex with curcumin designed to enhance its oral bioavailability [35]. The first study, a short-term product registry study, showed that the group receiving Meriva had improvements in pain sensation, joint stiffness, and physical function according to their WOMAC scores [36]. The second study aimed to assess the long-term efficacy and safety of Meriva in subjects with OA [37]. In this study, subjects in both the control group, which was defined as the "best available treatment," and the treatment group, which was the "best available treatment plus Meriva," could use NSAIDs during the study to control their pain if needed. Subjects from the treatment group had improvements in pain, stiffness, and physical function according to their WOMAC scores, improved Karnofsky performance scores, and statistically significant reductions in serum concentrations of sCD40L, IL-1 $\beta$ , IL-6, and ESR. Additionally, the treatment group showed a 63.4% decrease in NSAIDs use compared with 8% in the control group and a 63.5% decrease in health care costs compared with 3.7% in the control group. This study suggested that curcumin might be used instead of NSAIDs. This option would be especially attractive for subjects who cannot tolerate NSAIDs, have a history of adverse gastrointestinal and renal effects, or simply wish to take more natural substances.

Moreover, a proprietary lecithin formulation of curcumin (Meriva) was shown to reduce acute pain subjects with various chronic states [38]. Meriva supplementation (2.0 g) exerted proven analgesic activity comparable with acetaminophen (1.0 g) but lower than nimesulide (100 mg). Worth stressing is that gastrointestinal tolerance was much better than in the case of nimesulide and comparable with acetaminophen. Although this Meriva dose was definitely larger than that administered in persistent inflammatory disorders (1.0 – 1.2 g per day), Meriva pain-relieving properties could be associated with anti-inflammatory effects induced by curcumin in such an increased dose.

Another interesting aspect is the delayed onset muscle soreness (DOMS) evoked by eccentric muscle activity. DOMS is linked with the inflammatory response and reactive oxygen species synthesis. Drobic et al. assessed in a randomized, placebo-controlled trial the hypothesis whether curcumin had the potential to diminish tissue injury due to inflammation and oxidative stress associated with the eccentric continuous exercise [39].

Twenty male moderately active healthy volunteers were enrolled to curcumin (200 mg twice per day) or placebo. Curcumin administration was launched two days prior to the downhill running test and maintained 24 hours after the test (in total – 4 days). Subjects taking curcumin reported less lower limb pain than placebo group subjects. Moreover, significantly fewer subjects in the curcumin group revealed evidence of muscle damage in MRI. This study suggested that curcumin might bear a potential role in preventing DOMS, as indicated by its impact on pain intensity and muscle injury.

Di Pierro et al. observed similar findings in rugby players [40]. Fifty rugby players with musculoskeletal pain in the course of traumatic injuries, physical overload, or acute episodes of chronic pain were enrolled. They received standard analgesic drugs ( $n = 25$ ) or Meriva-based supplement ( $n = 25$ ) for maximally 10 days. The pain perception and the functions were evaluated at baseline and after 1, 3, 6, 10, and 20 days from the treatment initiation. Authors concluded that curcumin-based supplements could stand as a safe and promising alternative in painful musculoskeletal disorders in subjects exposed to intense physical activities.

Belcaro et al. also confirmed that the 4-month supplementation of glucosamine together with Meriva could promote the faster onset of action and better outcomes than using the combination of glucosamine and chondroitin sulfate in subjects with OA [41].

Moreover, Franceschi et al. evaluated the impact of Meriva supplementation in otherwise healthy elderly subjects [42]. Several parameters (handgrip, weight lifting, time/distance before feeling tired after cycling, walking, climbing stairs; general fitness, proteinuria, oxidative stress, Karnofsky scale; left ventricular ejection fraction) were assessed at baseline and after three months. Authors proved that Meriva's addition to a standardized diet and exercise plan was associated with increased strength and physical performance in elderly subjects (sarcopenia prevention). Moreover, Riva et al. suggested that a curcumin-based supplementation combined with an appropriate lifestyle could prevent osteopenia in many cases [43].

To sum up, one should mention a systematic review by Onakpoya et al. The authors investigated the efficacy of curcuminoids administered orally in OA [44]. The authors included seven studies with a total number of 797 patients with primary knee OA. Curcuminoids administration, compared with placebo, significantly diminished knee pain ( $p < 0.01$ ) and improved quality of life ( $p < 0.01$ ). Curcuminoid use was also associated with significant improvements in WOMAC total scores as well as with substantial reductions in the use of rescue medication. The summary of curcumin properties is presented in Figure 1.

## BOSWELLIC ACIDS

*Boswellia serrata* is a tree encountered in mountainous areas of India, Middle East and Northern Africa. As stated

by Siddiqui “oleo gum-resin is tapped from the incision made on the trunk of the tree and is then stored in specially made bamboo basket for removal of oil content and getting the resin solidified. After processing, the gum-resin is then graded according to its flavor, color, shape and size. Gum-resin extracts of *Boswellia serrata* have been traditionally used in folk medicine for centuries to treat various chronic inflammatory diseases. The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids, responsible for anti-inflammatory properties” [45]. Recently researchers have verified the efficacy and safety of Boswellin, a novel extract of *Boswellia serrata* extract (BSE) containing 3-acetyl-11-keto- $\beta$ -boswellic acid (AKBBA) with  $\beta$ -boswellic acid (BBA) in a double-blinded, placebo-controlled trial [46]. The results proved that AKBBA and BBA exerted synergistic anti-inflammatory/anti-arthritic effects on physical and functional ability and decreased pain and stiffness.

## GINGER

Ginger (*Zingiber officinale*) is a traditional herb. Ginger is applied not only as a spice, but also used as a remedy to manage different ailments, e.g., musculoskeletal disorders, migraine, and even diabetes. There are two essential components, 6-gingerol and 6-shogaol, in ginger. They are responsible for preventing inflammation and oxidative stress [47]. In a randomized trial in elderly subjects with knee OA, authors disclosed that ginger supplementation was linked with decreased levels of TNF- $\alpha$  and IL-1 $\beta$  [48]. More recently, meta-analysis results showed that oral, but not topical, ginger was associated with pain relief in knee OA [49].

## NOVEL HERBAL COMBINATIONS

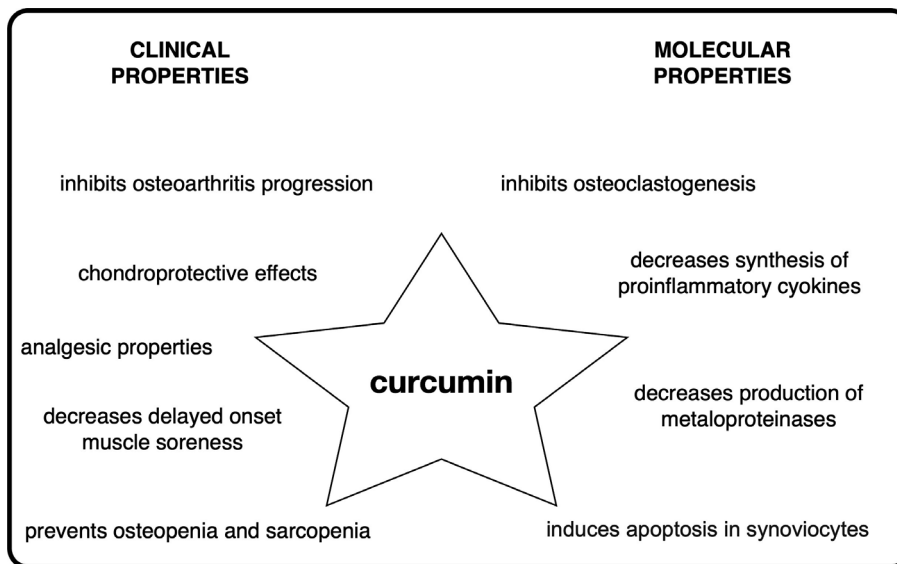
### CURCUMIN WITH BOSWELLIC ACIDS

Haroyan et al. proved that subjects taking curcuminoids combined with boswellic acids performed better than subjects taking placebo in physical performance tests and the WOMAC joint pain index. In contrast, when only the curcuminoid complex extract was used, it was more effective than placebo only in physical performance tests [50]. A further meta-analysis by Bannuru et al. confirmed that curcuminoids and *Boswellia* formulations might pose a valuable additive to the knee OA treatment regimens [51]. They effectively relieve pain symptoms and simultaneously reduce safety risks.

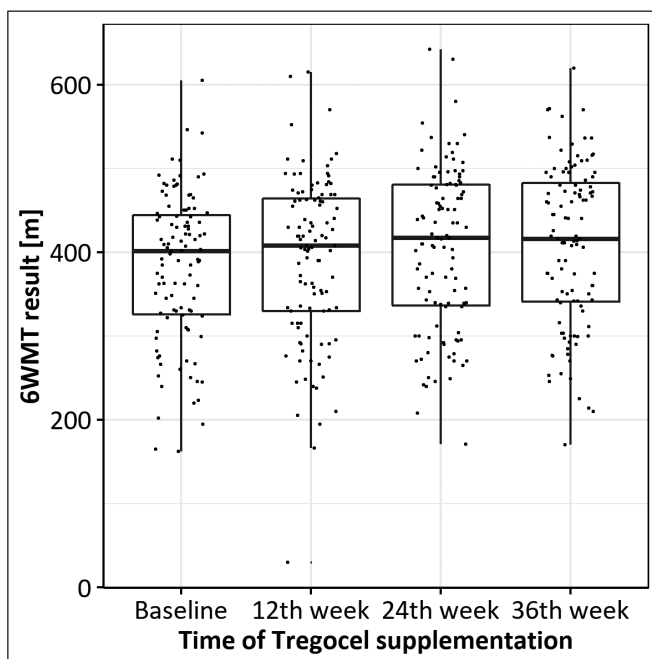
### GARLIC, CELERY, AND DEVIL'S CLAW

Garlic (*Allium sativum*) use was registered, among others, over 5000 years ago in Ayurvedic medicine, and over 3000 years ago in ancient China. The active substances enclosed in garlic include sulfur-containing elements such as alliin, substances derived from alliin (e.g., allicin) or enzymes (e.g., alliinase). Allicin is the key bioactive substance in

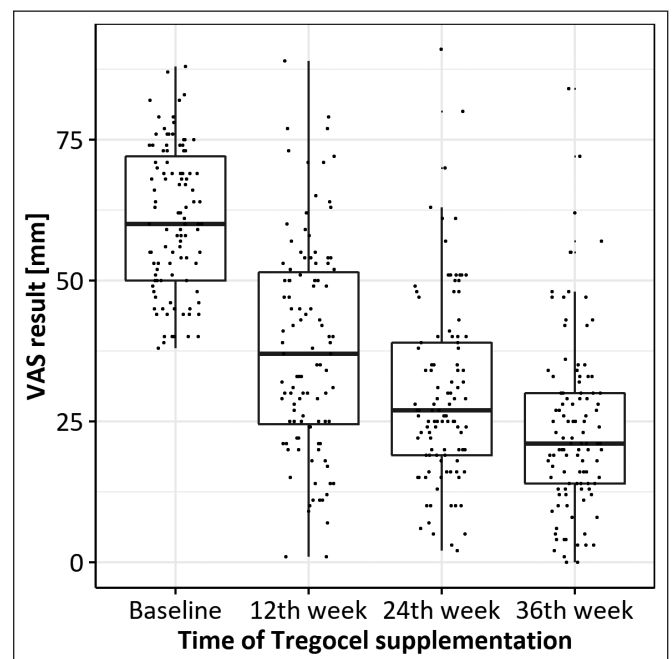




**Fig. 1.** Properties of curcumin.



**Fig. 2.** Results of 6-minute walk test (6MWT) at visit 1, visit 5 (after 12 weeks), visit 9 (after 24 weeks), and visit 13 (after 36 weeks). Results are presented as median with interquartile range (IQR).



**Fig. 3.** Pain assessment in VAS scale at visit 1, visit 5 (after 12 weeks), visit 9 (after 24 weeks), and visit 13 (after 36 weeks). Results are presented as median with interquartile range (IQR).

the garlic extract as well as raw garlic derivatives [52]. Dehghani et al. evaluated the anti-inflammatory and analgesic properties of garlic supplementation on pain severity and resistin and TNF- $\alpha$  serum levels in women with overweight or obesity and knee OA [53]. After 12 weeks, resistin levels were significantly reduced in the garlic group ( $6.41 \pm 2.40$  to  $5.56 \pm 2.16$  ng/mL;  $p < 0.01$ ). Similarly, pain scores were markedly decreased in the garlic group ( $6.8 \pm 2$  to  $5.3 \pm 2.3$ ;  $p < 0.01$ ), but not in the placebo group ( $6.7 \pm 2.4$  to  $6.2 \pm 2.5$ ;  $p = 0.67$ ). At the end of the study, the difference in pain scores was also statistically significant between groups ( $5.3 \pm 2.3$  vs.

$6.2 \pm 2.5$ ;  $p = 0.04$ ). The results confirmed that 3-month garlic supplementation might diminish pain severity in overweight or obese women with knee OA. Hedaya R proved the benefits of using celery's extracts, and Denner SS – devil's claw in OA [54, 55].

The main compounds of devil's claw are iridoid glycosides, such as harpagoside, harpagide, and procumbide. Interestingly, the devil's claw is used orally in folk medicine to treat a wide range of health conditions, including indigestion, fever, allergic reactions, and rheumatism. Additionally, other ethnomedicinal applications include urinary infectious, postpartum pain, ulcers, and inflam-

matory bowel diseases. Recently, it was shown that devil's claw was beneficial in rheumatoid arthritis (significant reduction in global pain and stiffness alongside with significant improvements in function and mean pain scores for hand, wrist, elbow, shoulder, hip, knee and back pain) as well as in osteoporosis (bone mineral density stimulation) [56].

### CURCUMINOIDS, BOSWELLIC ACIDS, CELERY SEED, DEVIL'S CLAW AND GINGER

An example of a novel supplement containing clinical levels of these key medicinal herbs is Tregocel<sup>®</sup>, which listed as a complementary medicine in Australia, and manufactured according to pharmaceutical GMP standards. The product is an herbal composite formulation that is designed to provide supportive benefits to standard pharmacotherapies for OA. It contains a patented curcuminoid preparation and standardized extracts of the herbs *Harpagophytum procumbens*, *Boswellia serrata*, *Apium graveolens*, and *Zingiber officinale*. Curcumin is an active phenolic compound found in turmeric (*Curcuma longa*). In Tregocel<sup>®</sup>, curcumin is incorporated into a phospholipid complex (Meriva<sup>®</sup>, Trademark of Indena, S.p.A.), which was shown previously to be 29-fold more absorbed than natural, unformulated curcuminoids [36]. It also contains a standardized extract of *Harpagophytum procumbens*, with several active compounds, including harpagosides as the primary compounds. Tregocel<sup>®</sup> also includes an extract of *Boswellia serrata*, in which boswellic acids are the primary active constituents. *Apium graveolens* (celery) seeds are other components, which contain volatile oils such as limonene and selinene, flavonoid compounds, celeroside glucosides, and phthalide glycosides, as well as aromatic and lignin glucosides. Finally, Tregocel<sup>®</sup> contains *Zingiber officinale* (ginger) extract, with the main phytochemicals as phenols (gingerol, shogaols, paradols), diarylheptanoids, gingerdiols, and sesquiterpenes [57].

An exploratory study with Tregocel<sup>®</sup> was performed in 2019 and assessed physical performance with a 6-minute walk test (6MWT) and WOMAC indices in participants with symptomatic mild knee OA (up to grade 2), as well as the perception of pain, general performance, level of standard pharmacological treatment and basic safety parameters, performed according to a registered clinical trial protocol [58]. One hundred and seven subjects completed a 36-week intervention across eight clinical sites in Poland. In brief, the intervention was associated with increased physical capacity and decreased pain. At baseline, the mean 6MWT distance was  $382.8 \pm 88.1$  m, and at the end of the study this had extended to  $408.8 \pm 96.3$  m. The increase of  $26.0 \pm 30.4$  m was statistically significant ( $p < 0.001$ ) (Figure 2). WOMAC scores assessed before the 6MWT in all domains (pain, stiffness, physical function, and total) had improved progressively throughout the study. The subsequent visits' scores were statistically significantly lower than initial values ( $p <$

$0.001$  for all comparisons). The decrease was the greatest after 12 weeks of Tregocel<sup>®</sup> supplementation (about 50% in all domains) and continued to improve in subsequent visits. With the duration of the study, subjective pain levels significantly decreased from baseline [60.0 (IQR 50.0 – 72.0) at baseline] to 37.0 (IQR 24.5 – 51.5) after 12 weeks of supplementation ( $p < 0.001$ ), 27.0 (IQR 19.0 – 39.0) after 24 weeks ( $p < 0.001$ ) and 21.0 (IQR 14.0 – 30.0) after 36 weeks ( $p < 0.001$ ). The overall decrease was statistically significant, and the value at the end of the study stood at approximately 30% of baseline pain scores (Figure 3). Concomitantly, a decrease in the requirement for standard medications was also observed. At baseline, 99.1% of patients regularly took anti-inflammatory/analgesic drugs, whereas this progressively declined after 12 weeks (76.6%), 24 weeks (69.2%), and 36 weeks (55.1%). As with previous trials of polyherbal supplements, the outcomes of this intervention are clinically meaningful for OA treatment, and integrate easily with standard therapies.

### CLINICAL IMPLICATIONS

Nutraceuticals in terms of being promising anti-inflammatory and antioxidant agents undergo extensive research studies. A growing body of evidence has suggested that many plants display robust pharmacological properties (anti-inflammatory, anti-catabolic, and anti-apoptotic), and that many of them are able of protecting joint cartilage against destructive processes. Furthermore, several studies have proved that the earlier mentioned pro-inflammatory cytokines are mostly regulated by the key transcription factor, i.e., NF- $\kappa$ B.

Analyzing the position of nutraceuticals in the management of subjects with knee OA, one must be stressed that we require new strategies and large-scale clinical trials that are supposed to take several years. Although we can identify some research revealing merit as well as nutraceuticals' efficacy comparable with NSAIDs, frequently these studies characterize small population, short follow-up or the lack of control group.

Nevertheless, nutraceuticals can become a very useful addition to pain relievers (e.g., NSAIDs), which are linked with various side effects and are used commonly in large quantities worldwide. Nutraceuticals might have their place especially in subjects with mild or moderate OA stages.

### CONCLUSIONS

Knee OA, the most frequent joint disorder, is linked with substantial health-care expenses, impaired productivity, as well as diminished quality of life. However, available pharmaceutical treatments have limitations in terms of efficacy and long-term safety. Results originating from several small studies with natural products in managing knee OA are encouraging and may allow for greater flexibility in clinical settings.

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# Conflict of interest:

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