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**Sharad Kamble**  
Assistant Professor,  
Department of Pharmaceutics,  
Nootan College of Pharmacy,  
Kavathe Mahankal, Sangli,  
Maharashtra, India

**Amol Patil**  
Head of Department, Nootan  
College of Pharmacy, Kavathe  
Mahankal, Sangli,  
Maharashtra, India

**Sunita Shinde**  
Assistant Professor,  
Tatyasaheb Kore College of  
Pharmacy, Warananagar,  
Kolhapur, Maharashtra, India

**Hrithik Ankush**  
Student, Nootan College of  
Pharmacy, Kavathe  
Mahankal, Sangli,  
Maharashtra, India

**Corresponding Author:**  
**Sharad Kamble**  
Assistant Professor,  
Department of Pharmaceutics,  
Nootan College of Pharmacy,  
Kavathe Mahankal, Sangli,  
Maharashtra, India

## A review on current nutraceuticals in the management of osteoarthritis

**Sharad Kamble, Amol Patil, Sunita Shinde and Hrithik Ankush**

### Abstract

Osteoarthritis (OA) is a progressive degenerative joint syndrome that has a major impact on joint function and quality of life. Nutraceuticals and nutritional supplement derived from herbs have long been used in traditional remedy and there is considerable evidence that nutraceuticals may play an important role in irritation and joint demolition in OA. We review the biological effects of some medicinal fruits and herbs like pomegranate, green tea, cat's claw, devil's claw, ginger, Indian olibaum, turmeric and ananas. So in an attempt to understand the essential molecular targets involved in irritation and the joint destruction process and to summarize their toxicities and efficacy for OA management. So far there is insufficient reliable evidence on the effectiveness of ginger, turmeric and ananas. Pomegranate and green tea only have preclinical evidence of efficacy due to the bee deficient in of clinical data. *In vivo* and clinical studies are required to understand their targets and efficacy in OA. There is strong clinical evidence of the efficacy of devil's claw in relieving pain. However, high-quality clinical trials are required to determine its effectiveness. No severe side effects have been reported for any fruits and herbs. Overall, these studies discover and support the use of nutraceuticals to provide symptomatic relief to patients with OA and to be used as accessory therapy for OA management. More high-quality trials are needed to provide perfect answers to questions related to their efficacy and safety for OA prevention and/or treatment.

**Keywords:** osteoarthritis, nutraceuticals, ginger, turmeric, articular cartilage, inflammation of synovium

### Introduction

Osteoarthritis (OA) is one among the foremost prevalent and disabling chronic diseases affecting older people. A high prevalence of OA among older people and ladies and therefore the moderate to severe impact on lifestyle pose a big public ill health. OA involves the erosion of articular cartilage, inflammation of synovium, and resorption of the underlying subchondral bone. These pathological changes are related to an excessive production of proinflammatory molecules like interleukin 1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), which shift the balance between the synthesis and degradation of matrix components leading to progressive destruction of the joint tissue.

Today, a cure for OA remains elusive. Nonpharmacological management includes physiotherapy, aerobic exercises, muscle strengthening, weight reduction, walking aids, knee braces, footwear and insoles, electromagnets, thermal modalities and acupuncture. For OA treatment and prevention, glucosamine and chondroitin sulfate, two of the molecular building blocks found in articular cartilage, are the foremost commonly used dietary supplements. In randomized trials of variable quality, these compounds show efficacy in reducing symptoms, but neither has been shown to arrest progression of the disease or regenerate damaged cartilage. Pharmacological management of OA has targeted symptoms of the disease instead of the underlying cause; analgesics and nonsteroidal anti-inflammatory drug drugs (NSAIDs) represent the mainstay of treatment [Altman, 2009]. These drugs generally decrease pain and stiffness and improve function. Although, any beneficial effects to the underlying cartilage and bone associated with the use of these drugs have not been demonstrated, they remain among the most widely prescribed drugs for OA therapy [1].

The term 'nutraceutical' was coined from 'nutrition' and 'pharmaceutical' in 1989 by DeFelice and was originally defined as 'a food (or a part of the food) that gives medical or health benefits, including the prevention and/or treatment of a disease. Zeisel distinguished whole foods from the bioactive chemical compounds derived from them and available during a nonfood matrix by using the terms 'functional foods' and 'nutraceuticals' respectively.

However, the term nutraceuticals has no regulatory definition and isn't recognized by the US Food and Drug Administration (FDA), which uses the term 'dietary supplements' instead. OA as a chronic disease may be a perfect paradigm of pathology of treatment, which might be addressed by nutraceuticals and dietary supplements. First, because nutraceuticals only have limited effects on their biological target and significant differences are often reached over time through a buildup effect during which daily benefits add up and the time window for intervention is longer in chronic diseases. Second, nutraceuticals could provide a safer alternative because generally their use is barren of adverse effects, although this is often not universal. Public interest in the benefits provided by nutraceuticals such as medicinal herbs for OA is high and 47% of older adults use nonprescribed alternative medications (dietary supplements) for OA management [2, 3]. The objective of this review is to debate the scientific evidence supporting the efficacy of *Punica granatum* (pomegranate fruit), tea (green tea), *Uncaria tomentosa*/ *Uncaria guianensis* (cat's claw), *Harpagophytum procumbens* (devil's claw), common ginger (ginger), salai, turmeric (turmeric) and *Ananascomosus* in an effort to know the pivotal molecular targets involved in inflammation and therefore the joint destruction process and to summarize their toxicities and efficacies for OA management. We have purposely not considered use of glucosamine sulphate and chondroitin sulphate because these compounds are the most topic of various recent reviews. For this review a literature search was performed of the Pubmed database and the scientific data with a direct link to OA were selected. We tried to incorporate all the relevant references but the list might not be complete [4].

### ***Punica granatum* (pomegranate)**

Pomegranate fruit [PF, Figure 1] has been used for hundreds of years to confer health benefits in many cultures. It's native to semitropical Asia and is now being cultivated in Afghanistan, India, China, Russia, Japan and therefore the US. Modern use of PF-derived products includes treatment of AIDS [Lee and Watson, 1998], cancer, cosmetic use, allergic symptoms, cardiovascular conditions, oral hygiene and as ophthalmic ointment. Edible parts of the PF are composed of 80% juice and 20% seed. PF itself may be a rich source of two sorts of polyphenolic compounds: anthocyanins (such as delphinidin, cyanidin, and pelargonidin) and hydrolyzable tannins (such as punicalin, pedunculagin, punicalagin, gallagic, and ellagic acid esters of glucose), which account for 92% of the antioxidant activity of the entire fruit. Anthocyanins are potent antioxidants, provide the brilliant color of the pomegranate juice, and their administration is reported to significantly decrease the malondialdehyde, hydroperoxide levels, lipid peroxidation and also enhance the activities of catalase, SOD, peroxidase and glutathione reductase within the liver. Punicalagin has been shown to downregulate the expression of IL-2 from anti-CD3/anti-CD28-stimulated murine splenic CD4+ T cells and suppress mixed leukocyte reaction without exhibiting cytotoxicity to the cells via inhibition of nuclear factor of activated T cells. This means that PF might be a possible candidate for the therapeutics of immune pathologies. We reported that pomegranate fruit extract (PFE)-derived bioavailable compounds suppress COX-2 enzyme activity and IL-1 $\beta$ -

induced prostaglandin E2 (PGE2) and gas (NO) production in OA chondrocytes [5]. We showed the inhibitory effects of PFE on IL-1 $\beta$ -induced proteoglycan breakdown in cartilage explants *in vitro*. We also studied the efficacy of PFE in suppressing joint inflammation and damage employing a collagen-induced arthritis mouse model. Consumption of PFE potentially delayed the onset and reduced the incidence of collagen-induced arthritis in mice. Histopathology of the arthritic joints from PFE-fed mice demonstrated reduced joint infiltration by the inflammatory cells, and therefore the destruction of bone and cartilage was alleviated with the decrease level of IL-6. Activation of mitogen-activated protein kinases (MAPKs) and nuclear factor (NF)- $\kappa$ B is intimately related to the increased expression of critical mediators of inflammation involved in OA pathogenesis, including the expression of IL-6 and IL-8. We recently showed that inhibition of IL-6 and IL-8 by PFE in PMACI (phorbol12-myristate 13-acetate plus calcium ionophore A23187)-stimulated KU812 cells was mediated by inhibition of NF- $\kappa$ B, cJun-N-terminal kinases (JNKs) and therefore the extracellular regulated kinase (ERK)-MAPK pathway [6]. We also showed that PFE (6.25–25 mg/liter) inhibits the IL-1 $\beta$ -induced expression of MMP-1, MMP-3 and MMP-13 mRNA and proteins in OA chondrocytes, which was mediated by inhibiting the activation of p38-MAPK and JNK, thereby reducing the available pool of activated c-Jun and activating transcription factor 2. Our recent study showed that PFE inhibits the IL-1 $\beta$ -induced activation of MKK3 and therefore the p38 $\alpha$ -MAPK isoform and DNA binding activity of the runt-related transcription factor 2 in human chondrocytes. These results provide a crucial insight into the molecular basis of the reported cartilage protective and arthritis inhibitory effects of pomegranate.

Overall, these data indicate that consumption of PF could also be beneficial and useful in developing adjunct preventive and/or therapeutic approaches to the prevention and treatment of OA. However, clinical trials showing the advantage of pomegranate fruit or its extracts on inflammation and OA are lacking. supported published evidence, further *in vivo* evaluation and clinical testing for the efficacy of PF in OA are needed [6, 7, 8, 9].



**Fig 1: *Punica granatum***

### ***Camellia sinensis* (green tea)**

Tea may be a widely consumed beverage throughout the planet and is reported to possess significant health-promoting effects. Green tea [Figure 2] contains proteins (15%), amino acids (4%), fiber (26%), other carbohydrates (7%), lipids (7%), pigments (2%), minerals (5%), and phenolic compounds (catechins; 30%). The principal

catechins found in tea are epicatechin (6.4%), epicatechin-3-gallate (13.6%), epigallocatechin (19%) and epigallocatechin-3-gallate (EGCG; 59%), and account for 30–40% of its dry weight. Green tea catechins, especially EGCG, have been reported to have antimutagenic, anticancer, antidiabetic, antiinflammator, antibacterial, antiviral, antiobesity and neuroprotective effects [10, 21]. The strong antioxidant activity of tea catechins has been widely demonstrated *in vitro* and *in vivo*. Several studies have shown that EGCG blunts reactive oxygen species (ROS) mediated cytotoxicity in human chondrocytes. EGCG has been reported to increase the activities of catalase, superoxide dismutase, and glutathione peroxidase, which are essential components of a robust antioxidant defense system [11].

High levels of nitrates/nitrites are found within the synovia and serum of patients with OA. Studies from our laboratory have shown that EGCG inhibits NO production in IL-1 $\beta$ -stimulated human OA chondrocytes by suppressing the expression of inducible nitric oxide synthase (iNOS) mRNA, which was mediated in part by inhibition of NF- $\kappa$ B/p65. COX-2 is the rate limiting enzyme in the production of PGE2 and we reported that EGCG inhibited the PGE2 production via inhibition of COX-2 expression in IL-1 $\beta$ -stimulated human OA chondrocytes. However, Koeberle and colleagues reported that microsomal prostaglandin-E synthase 1 (mPGES1) is a molecular target of EGCG, and inhibition of mPGES-1 is seemingly the predominant mechanism underlying suppression of cellular PGE2 biosynthesis by EGCG *in vitro*. Age-related accumulation of advanced glycation end products (AGEs) produced by the nonenzymatic glycation of macromolecules could be an important contributing factor for the development of OA. We recently reported that EGCG inhibited AGE-stimulated expression and production of TNF $\alpha$  and MMP-13 and this inhibitory effect was mediated a minimum of partially via suppression of p38-MAPK, JNK, and NF- $\kappa$ B activation in human OA chondrocytes. EGCG has also been reported to inhibit the degradation of human cartilage proteoglycan and type II collagen and selectively inhibit the expression of ADAMTS-1, -4 and -5 (A Disintegrin And Metalloproteinase with Thrombospondin Motifs), which are known to cleave aggrecan. Previously we showed that EGCG significantly inhibited the expression and activities of MMP-1 and MMP-13 in OA chondrocytes at physiologically achievable doses. We and others have also shown that EGCG inhibits NF- $\kappa$ B activation by inhibition of proteasome activity, inhibition of I $\kappa$ B $\alpha$  phosphorylation or inhibition of IKK- $\beta$  kinase activity in human OA chondrocytes. We have also shown that EGCG selectively inhibited IL-1 $\beta$ -induced activation of JNK, without significantly inhibiting the phosphorylation of p38-MAPK or ERK p44/ p42 in human OA chondrocytes. Activator protein (AP)-1 transcription factor is a heterodimer of Jun and Fos proteins and plays an important role in the inflammatory response. EGCG was found to inhibit the activation and DNA binding activity of AP-1 in human OA chondrocytes. This could be overcome by repeated administration of EGCG due to its reported low toxicity and high tolerance by humans, even when given in doses as high as 1600 mg, which can achieve a maximum human plasma level of 7.6  $\mu$ mol/liter. These studies mean that a pharmaceutically prepared formulation of tea catechins

could reach plasma levels like effective *in vitro* doses and may be used as adjunct therapy for the treatment and prevention of OA. Currently, there's sufficient *in vitro* and *in vivo* data available showing the anti-inflammatory and antiarthritic potential of tea and its constituent EGCG. Hence, more *in vivo* and clinical studies are required to gauge its efficacy for OA. [12, 13, 14]



Fig 2: Camellia sinensis

#### ***Uncaria tomentosa* and *Uncaria guianensis* (cat's claw)**

Cat's claw may be a vine from the basin of the Amazon. There are two species, *U. tomentosa* [Figure 3A] and *U. guianensis* [Figure 3B] that are traditionally used in South America for their antiinflammatory properties. Cat's claw bark contains oxindole alkaloids (virtually absent in *U. guianensis*), polyphenols (flavonoids, proanthocyanidins, and tannins), quinovic acid  $\alpha$ -glycosides, pentacyclic alkaloids, and sterols. Traditionally, the bark of cat's claw is prepared as a decoction, said to be beneficial in the treatment of arthritis, bursitis, lupus, chronic fatigue syndrome, and for stomach and intestine disorders. The most investigated of the active constituents in *U. tomentosa* extract for immune-modulating and anti-inflammatory effects are pentacyclic oxindole alkaloids. However, the antioxidant and anti-inflammatory effects of the extracts of *U. tomentosa* and *U. guianensis* appear to be independent of their alkaloid content as in several assays both species of *Uncaria* were reported to be a robust radical scavenger. We reported that *U. guianensis* together with *Lepidium meyenii* had ch"art-10">This action was mediated partially through upregulation of organic phenomenon of the anabolic insulin-like protein 1 in IL-1 $\beta$ -stimulated chondrocytes [15]. Pretreatment with a hydroalcoholic extract (500  $\mu$ g/ml) of *U. tomentosa* inhibited COX-1 and COX-2 via inhibition of the activation of NF- $\kappa$ B in Jurkat T cells. *Uncaria* has been found to inhibit lipopolysaccharide (LPS)-induced iNOS gene expression, TNF $\alpha$ , PGE2 and NO production, and cell death via inhibiting the activation of NF- $\kappa$ B. Recent studies support the use of *Uncaria* alone or in combination with other medicinal herbs for OA management. The available animal toxicological data didn't indicate any severe toxicity by the oral intake of *Uncaria*. In some cases, mild nausea and diarrhea may occur upon ingestion of crude extracts. Several other groups have documented the security and pharmacological profile of cat's claw in animal models and also showed that cat's claw was non-toxic *in vitro*. In another study, a mixture of a natural mineral supplement (Sierrasil, Sierra Mountain Minerals Inc., Bozeman, MT, USA) with a cat's claw extract (*Vincaria*, Rainforest

Nutritionals Inc., Raleigh, NC, USA) showed therapeutic potential in mild to moderate knee OA. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analog scale (VAS) scores were improved after 8 weeks compared with placebo. Rescue medication use was 28–23% lower in the herbomineral combination. Comparison of Reparagen (Rainforest Nutritionals, Inc., Raleigh, NC, USA) (1800 mg/day), a mix of *U. guianensis* and *L. meyenii* with glucosamine sulfate (1500 mg/day) was also studied in patients with OA during a multicenter, randomized, double-blind trial. Reparagen and glucosamine sulfate produced substantial improvements in pain, stiffness and performance in patients with mild to moderate OA as evidenced by improved WOMAC and VAS scores [16].



Fig 3A: *Uncaria tomentosa*



Fig 3B: *Uncaria guianensis*

#### ***Harpagophytum procumbens* (devil's claw)**

For more than 50 years preparations of *H. procumbens* [devil's claw, Figure 4] are utilized in Europe for the treatment of rheumatic entities. Devil's claw is native to the southern part of the African continent and should be found in Namibia, Botswana, South Africa, Angola, Zambia, and Zimbabwe. Historically, devil's claw has been used as an analgesic, for fevers and allergies, appetite stimulation, wounds and skin rashes, dyspepsia, liver and kidney disorders, as diuretic and sedative, and to treat degenerative disorders of the musculoskeletal system. The major chemical constituents of devil's claw are iridoid glycosides (primarily harpagoside, harpagide, and procumbide), sugars (mainly the tetrasaccharide, stachyose), triterpenoids (oleanolic and ursolic acid), phytosterols (primarily  $\beta$ -sitosterol), aromatic acids (caffeic, cinnamic, and chlorogenic acids), and flavonoids like luteolin and

kaempferol. Harpagoside, harpagide, and procumbide, found within the tubers of the plant, appear to be the foremost therapeutically important constituents. Wholeplant extracts appear to possess a far better therapeutic effect than those prepared from isolated parts. The flavonoids and plant phenols present in devil's claw extracts could also be the constituents liable for the observed antioxidant activity. Devil's claw has been found to scavenge both superoxide and peroxy radicals. A recent study also showed that both root tuber extract of devil's claw and tincture are effective as radical scavengers and inhibit LPS-induced nitrite levels in RAW 264.6 macrophages. Significant antioxidant effects by an aqueous extract of devil's claw and by the flavonoid constituents luteolin and kaempferol have also been noted. A dried aqueous extract (5 and 10 mg/kg) of devil's claw has been shown to exert a significant dose-dependent analgesic and anti-inflammatory effect in rats. However, carrageenan-induced paw edema wasn't suffering from harpagoside, suggesting harpagoside might not have an anti-inflammatory effect a minimum of within the doses utilized *in vivo*. *In vitro* data also demonstrated that the active principle (sum of coactive constituents) of devil's claw inhibits not only inflammatory mediators such as iNOS and COX-2 mediated PGE2 production or leukotriene release. Devil's claw extract appears to be safe when utilized in appropriate dosages. The side effects are few, usually limited to gastrointestinal upset, dyspepsia and loss of taste; no long-term toxicities or drug-interactions are known. Devil's claw extract exerts a peripheral analgesic effect because it has been demonstrated to decrease pain in knee and hip OA. The effectiveness of certain devil's claw preparations has been tested with a daily dose of 360 mg of harpagoside (a coactive ingredient) in the treatment of painful OA of the hip, knee and nonspecific low back pain. Multivariate analysis confirmed that in all groups, both the generic and disease-specific outcome measures improved by week 4 and further by week 8. *H. procumbens* powder was equally effective as diacerhein in reducing pain as measured employing a 100 mm VAS. This study constitutes moderate evidence that 4 months' daily use of 2610 mg *H. procumbens* powder is not significantly different from 100 mg diacerhein, producing comparable improvements in pain. Studies on devil's claw extracts, containing 50–100 mg harpagoside daily, have shown the simplest results. In a clinical study, 89 patients with OA were randomized to receive placebo or devil's claw at a complete daily dose of 2010 mg/day for 8 weeks. The study identified that after 30 and 60 days of treatment, patients who received devil's claw had a big reduction in pain ( $p = 0.018$  after 30 days and  $p = 0.012$  after 60 days of treatment) compared with placebo. Effectiveness, safety and tolerability of *Harpagophytum* was studied in rheumatic disorders including OA for 8 weeks (259 patients). There were statistically significant ( $p < 0.0001$ ) improvements in patient assessment of global pain, stiffness, function and quality of life. There were also statistically significant reductions in mean pain scores for hand, wrist, elbow, shoulder, hip, knee and back pain. Unfortunately, the results of many of the studies are of questionable value because of methodological flaws. However, devil's claw appears to be effective in the reduction of pain. More high-quality trials are needed to assess the effectiveness and efficacy of devil's claw to determine whether this is a beneficial remedy for the treatment of OA [17].



Fig 4: *Harpagophytum procumbens*

### ***Zingiber officinale* (ginger)**

Ginger, the rhizome of *Z. officinale* [Figure 5], is one among the foremost widely used species of the Zingiberaceae (Zingiberaceae) and may be a common condiment for various foods and beverages. Ginger features a long history of medicinal use dating back 2,500 years in China and India for conditions like headaches, kinetosis, nausea, vomiting, vascular conditions, cold and arthritis, and as an antimicrobial and antifungal. Characterized in traditional Chinese medicine as spicy and hot, ginger is claimed to warm the body and treat cold extremities, improve a weak and tardy pulse, address a pale complexion, and strengthen the body after blood loss [18]. The major constituents of ginger include volatile oils, oleoresin (gingerol), linolic acid and trace elements like magnesium, phosphorus, and potassium [19]. The pungent phenolic constituent of ginger, [6]-gingerol, inhibited LPS-induced iNOS expression and production of NO and other reactive nitrogen species in macrophages and blocked peroxynitrite-induced oxidation and nitration reactions *in vitro*.

Ginger is on the US FDA's generally recognized as safe (GRAS) list. The British Herbal Compendium documents no adverse effects of ginger consumption. A randomized, placebo-controlled, crossover study comparing ginger extracts and ibuprofen was performed and included 75 people with OA of the hip or knee. Patients received 170 mg ginger extract, 400 mg ibuprofen, or placebo 3 times per day and were followed for 3 weeks. The study revealed significant improvement in symptoms for both groups before crossover; however, at the study's end there was no difference between ginger and placebo. No side effects were noted within the ginger group. A randomized, double-blind, placebo-controlled trial studied the consequences of ginger within the treatment of knee OA in 261 patients. During the treatment period patients ingested 255 mg of EV.EXT 77, a patented ginger and galangal, a spice that's closely associated with ginger and is of the ginger extract, which contained 500–4000 mg of dried ginger rhizomes and 500–1500 mg of dried galangal rhizomes and was given twice daily. The primary endpoint of the study was pain on standing after 6 weeks. Within the ginger extract group 63% versus 50% within the placebo group showed improvement. The study did not show improvement in quality of life, decrease within the consumption of the rescue analgesic (acetaminophen). The dosage of medicines utilized in this study was based empirically on what's typically consumed in Europe. Those receiving the ginger extract experienced more

gastrointestinal side effects (116 events in 59 patients, 45%) than those that received placebo (28 events in 21 patients, 16%). While a big number of patients experienced side effects, they were mild and mostly gastrointestinal conditions, dyspepsia, and nausea. In some studies, consumption of ginger extract was found to alleviate pain and associated symptoms in patients with OA. at the present, ginger extract appears to be of limited efficacy for OA and current evidence is weak. However, these results are strong enough to advocate and support further studies using different doses and duration of treatment to assess the efficacy of ginger extract alone or together with other drugs for the treatment of OA [20].



Fig 5: *Zingiber officinale*

### ***Boswellia serrata* (Indian olibaum)**

The *Boswellia* spp., which is native to India, Ethiopia, Somalia, and therefore the Arabic peninsula, produce a natural resin that's referred to as olibanum (frankincense). The resin of *B. carteri* and *B. serrata* [Figure 6] is used for the treatment of arthritis and other inflammatory diseases in the traditional medicine system in many countries. Besides their renowned anti-inflammatory activity, boswellic acids are extensively investigated for his or her chemopreventive effects [20]. *B. frereana* extracts have also been reported to inhibit IL-1 $\beta$  and oncostatin M induced MMP-9 and MMP-13 expression in cartilage explants culture. Further, boswellic acids have been reported as inhibitors of 5-lipoxygenase, the key enzyme for leukotriene biosynthesis in inflammatory disorders and human leukocyte elastase a member of serine proteases subfamily, which can hydrolyze collagen IV and elastin of the extracellular matrix [21]. Thus, its use could also be beneficial in inhibiting the progression of OA. Recently, we studied the efficacy of a herbal-leucine mix (HLM) containing *B. serrata* as one of the constituents. HLM was found to be an effective antiinflammatory agent, as evidenced by strong inhibition of iNOS, MMP-9 and MMP-13 expression and NO production in IL-1 $\beta$ -stimulated OA chondrocytes *in vitro*. IL-1 $\beta$ -induced cartilage matrix breakdown was also inhibited by HLM, as evidenced by inhibition of glycosaminoglycan (GAG) release from human cartilage explants *in vitro*. These inhibitory effects of HLM on the inflammatory and cartilage catabolic factors were mediated by inhibiting the activation of NF- $\kappa$ B in human OA chondrocytes. A novel composition of *B. serrata* extract (Aflapin, Indian Patent Application No. 2129/CHE/2008) showed anti-inflammatory and antiarthritic potential during a rat model. Aflapin showed significant protection from IL-1 $\beta$ -induced death of human primary chondrocytes,

improved glycosaminoglycans production and inhibited MMP-3 production [22].

A randomized clinical test of multiplant ayurvedic drugs containing *B. serrata* demonstrated the potential efficacy and safety within the symptomatic treatment of knee OA over 32 weeks of therapy. *B. Serrata* extract alone with O-acetyl-11keto- $\beta$ -boswellic acid (AKBA) (Aflapin) or AKBA (30%; Loxin) alone was tested in patients with knee OA. Both treatments were effective in reducing pain and significantly improved physical functioning and stiffness scores. However, Aflapin was more effective than Loxin. In a double-blind, placebo-controlled trial, *Boswellia* demonstrated a beneficial effect on knee OA. Thirty patients got either 1000 mg *Boswellia* daily or placebo in three divided doses for 8 weeks. Patients in the *Boswellia* group experienced a significant decrease in pain and swelling and increase in range of motion compared with placebo. *B. serrata* extract containing 5-Loxin with 3-O-acetyl-11-keto- $\beta$ -boswellic acid (30%) inhibited the 5-lipoxygenase enzyme. A 90-day, placebocontrolled study was conducted to evaluate the efficacy and safety of 5-Loxin in the treatment of OA of the knee with 75 patients. The patients received either 100 mg (n = 25) or 250 mg (n = 25) of 5-Loxin daily or a placebo (n = 25) for 90 days. Both doses of 5-Loxin conferred clinically and statistically significant improvements in pain scores and physical function scores in patients with OA. A significant reduction in synovia MMP-3 was also noted [23].



Fig 6: *Boswellia serrata*

### Conclusion

It concluded that, Pomegranate and green tea only have preclinical evidence of efficacy due to the bee deficient in of clinical data. *In vivo* and clinical studies are required to understand their targets and efficacy in OA. There is strong clinical evidence of the efficacy of devil's claw in relieving pain. However, high-quality clinical trials are required to determine its effectiveness. No severe side effects have been reported for any fruits and herbs. Overall, these studies discover and support the use of nutraceuticals to provide symptomatic relief to patients with OA and to be used as accessory therapy for OA management. More high-quality trials are needed to provide perfect answers to questions related to their efficacy and safety for OA prevention and/or treatment.

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