

# Unravelling the Approaches to Treat Osteoarthritis: A Focus on the Potential of Medicinal Plants

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## ABSTRACT

**Background:** Osteoarthritis (OA) is the most prevalent chronic rheumatic disorder, affecting more women than men. The prevalence and course of OA are increased by ageing and obesity. Numerous other risk factors for OA progression include oxidative stress, injury, mechanical stress, and metabolic problems. Interleukin-1 is released during inflammatory responses, which destroys cartilage. Interleukin-1 is correlated with the release of proteases, an enzyme that destroys cartilage further. Other cytokines similar to TNF- $\alpha$  induce the enzyme matrix metalloproteinases (MMP), which causes joint injury. Collagenase is another enzyme that degrades collagen and so impacts negatively on the articular cartilage. NSAIDs, opioid analgesics, topical analgesics, and intra-articular steroids are being used to alleviate osteoarthritis pain, and symptoms. However, various adverse effects are linked with all of these medications, limiting their usage, for example, NSAIDs used to relieve OA pain. Nonetheless, they exhibit gastrointestinal, cardiovascular, and nephrotoxicity. Tramadol also has an effect on the central nervous and gastrointestinal systems. Patients were interested in herbal plants because they were worried about the safety and inadequate effectiveness of pharmaceuticals. Plants have been used to cure a variety of ailments since ancient times, and several plants have the ability to treat OA. According to several studies, the pain and progression of OA may be considerably slowed, or halted by bioactive chemicals found in plants. **Conclusion:** Here we analysed the current scientific literature available that revealed a rising number of research on the possible antiosteoarthritic effects of medicinal plants and their principal ingredients, indicating the possibility of a novel therapeutic use.

**Keywords:** Antiosteoarthritic, Chondrocytes, Herbal plants, Cartilage, Inflammation, Collagenase.

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**Received:** 03-Aug-2022 ; **Revised:**  
08-Oct-2022 ; **Accepted:** 07-Nov-2022

## INTRODUCTION

Arthritis is the major cause of disability and joint pain in the elderly, and it is the most prevalent health condition in the world. The most prevalent sites of inflammation are the knees, feet, hands, hips, and lower back. Rheumatoid arthritis (RA) and osteoarthritis (OA) are the two most frequent forms of arthritis, although there are many more OA. Both deteriorate joint structures and produce excruciating pain, but their signs,

causes, and treatments are very different. When the immune system assaults and inflames the joints, it is known as RA. When it comes to osteoarthritis, however, it's all about the deterioration of the articular cartilage as well as changes in the structure of the articular system.<sup>[1]</sup>

OA is the most prevalent chronic rheumatic disorder and affects women more than men. Ageing and obesity, and many more factors like oxidative stress, injury, mechanical stress, and metabolic disorders increase the prevalence, and progression of OA. Influence OA progression. It is characterised by cartilage degeneration and synovitis changes (Figure 1). OA affects mainly the knee joints, and it is estimated that around 12% of patients are concerned with knee OA, 6.8% affects with OA of the hands, and



DOI: 10.5530/097484900001

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about 9.2% are affected by OA of the hip joint.<sup>[2]</sup> OA influences the quality of a patient's life by the loss of physical structure and the failure of all joint functions. In OA, the most prominent is loss of articular cartilage, but a synovial membrane, subchondral bone, and ligaments are also affected. On the cellular level, catabolic functions of chondrocytes overcome the anabolic processes of chondrocytes which pro-inflammatory mediators stimulate. These mediators are localised in synovial fluid and stimulate the production of enzymes like collagenase and aggrecanases, which degrade collagen, and proteoglycans. There are several mediators, such as IL-1, NO, TNF-, PGE2, NF-B, and mitogen-activated protein kinase signalling pathways, that play an important part in the pathophysiology of OA. Pain, soreness, and stiffness are all indications of OA, which progresses slowly.<sup>[3,4]</sup>

Osteoarthritis is a debilitating disease that has few effective therapeutic options. Osteoarthritis is now treated with NSAIDs, an opioid analgesic, a topical analgesic, and intra-articular steroids to reduce pain, and symptoms. There are several side effects associated with all these treatments, including gastrointestinal, cardiovascular, and nephrotoxicity, tramadol, indomethacin, and NSAIDs, which all limit their use in OA.<sup>[5,6]</sup> As a result, patients began to express an interest in herbal plants due to concerns regarding safety, and effectiveness. Aside from that, people have relied on plant-based medications for centuries because of the lower risk of adverse effects. For this reason, a variety of herbal medicines were used. Even so, they don't completely treat OA, but they may be quite successful if the proper diet, and therapy are used. The pain and inflammation associated with OA may also be reduced by using some medicinal herbs.<sup>[7,8]</sup> Herbal plants as a treatment option for OA are the focus of this review, which intends to offer current research, and demonstrate the potential of medicinal plants to alleviate OA symptoms.

## Pathophysiology

OA is the most common type of joint disorder. It is a worn and tears disease. The excessive reaction of chondrocytes and inflammatory mediators is responsible for the breakdown of

articular cartilage in OA pathogenesis. In addition to cartilage and the synovial membrane, OA affects bones, and the subchondral bone.<sup>[9]</sup>

Steps involved in the degradation of articular cartilage: stage 1 involves the breakdown and conversion of cartilage proteins into amino acids and polypeptides takes place. Fibrillation or erosion occurs as a result of protein fragments leaking into the synovial fluid in stage 2. Articular cartilage is further degraded by the first two stages of inflammation.

Articular cartilage, also known as hyaline cartilage, is located at the ends of bones, and is affected by OA. In cartilage, collagen, and glycosylated proteins are the primary building blocks that hold the tissue together. The cartilage also contains chondrocytes.<sup>[10]</sup> When there is an inflammatory reaction, interleukin-1 is released, which damages cartilage. IL-1 is linked to the release of protease enzymes that further breakdown cartilage. TNF-alpha-like cytokines cause joint injury by activating the enzyme matrix metalloproteinases (MMPs). Colloidal collagenase is another enzyme that degrades articular cartilage (Figure 2).<sup>[11]</sup>

The synovial membrane has an effect on the synovial fluid since it is a connective tissue. Inflammation of the membrane occurs as a result of cartilage injury. The articular cartilage is further damaged by synovial macrophages, which cause inflammation.<sup>[12]</sup>

## MATERIALS AND METHODS

Google Scholar, PubMed, and Scopus were used as academic search engines in the literature search. Essential oils, arthritis, antiarthritic, anti-rheumatoid arthritic activity, herbal plants, and chondroprotective agents were searched for in the databases. Studies on the antiarthritic properties of herbal plants, whether as whole plants, or as isolated active ingredients, are included in this review study.

## Potential medicinal plants for osteoarthritis treatment

Plants have long been used to treat a variety of illnesses, and a number of different plants have showed promise as OA-treating options. Plants may contain a bioactive component that reduces OA discomfort and development, according to several research. To treat various forms of arthritis, several species of plants have bioactive chemicals that may be extracted using alternative solvents (Table 1).

There are a number of plants that have the potential to cure OA, including *Boswellia serrata*, a member of the *Burseraceae* family, commonly known as *salai*. Different phytochemicals including monoterpenes (-thujene, -pinene, cis-verbena, transpinocarveol), diterpenes (Incensole and iso-incensole oxide), triterpenes (-amyrins), Boswellia acids, and tetracyclic triterpenic acids are found in the plant<sup>[13]</sup> Research demonstrates that *Boswellia serrata*

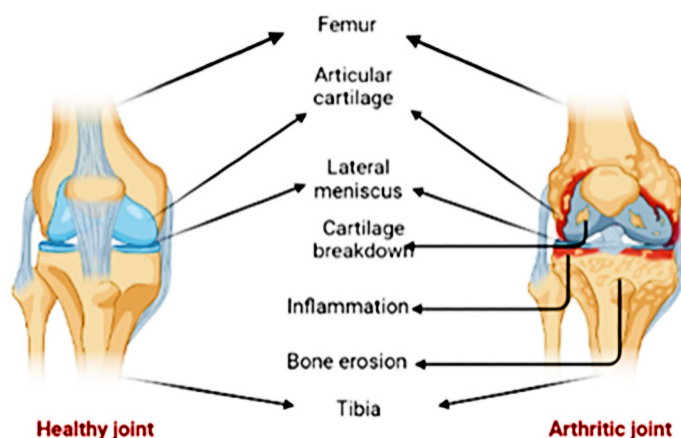


Figure 1: Healthy and osteoarthritic joint.

extract includes boswellic acid, a molecule that has been shown in trials to have OA-fighting properties. The anti-inflammatory and chondrocyte-protective characteristics of boswellic acid (Figure 3a) are shown by its ability to suppress the synthesis of the cytokines responsible for cartilage loss.<sup>[14–16]</sup> Boswellic acid was advised by the Arthritis Foundation to be taken in doses of 300–400 mg per day of *Boswellia*. OA may benefit from a combination of boswellic acid and curcumin, according to some research.<sup>[17]</sup> *B. serrata*'s, *B. aflapin* has also been shown to have anti-OA properties by blocking the MMP enzyme.<sup>[18–20]</sup>

Known as Du Zhong, *Eucommia ulmoides* is a tough rubber tree from the Eucomiaceae family. Lignans, iridoid glycoside, phenolic compounds, -sitosterol and daucosterol, ulmoprenol and betalin, betulinic acid, and ursolic acid are among the active phytochemicals found in the plant.<sup>[21]</sup> *E. ulmoides*' leaves and bark have been shown to have anti-OA properties. The phosphoinositol 3-kinase pathway prevents cartilage deterioration and reduces the production of inflammatory cytokines in *E. ulmoides* extract, however its effectiveness for OA is limited. There is some evidence to support the use of O-enriched *E. ulmoides* in the treatment of osteoarthritis.<sup>[22–24]</sup>

Cat's claw, or *Uncaria tomentosa*, is a pharmacologically active plant of the Rubiaceae family. Fever, UTI, viral infections, and wounds have all been traditionally treated with this herb, which contains anti-inflammatory alkaloids, flavonoids, sterols, and glycosides.<sup>[25,26]</sup> The cat's claw may also help alleviate osteoarthritis. Rhynchophylline (Figure 3b) is an indole alkaloid found in *U. tomentosa* extract that has been shown in studies to have substantial antioxidant and anti-inflammatory effects.<sup>[2,27,28]</sup>

Ashwagandha, a member of the Solanaceae family, is a popular name for *Withania somnifera*. Among the active phytochemicals in *Ashwagandha* include withanolide A, withanone, withanolide D, as well as alkaloids, flavonoids, steroids, and zingerone.<sup>[29]</sup> For OA and RA, *W. somnifera* has been utilised since ancient times. Due to withanolide, aqueous *W. somnifera* roots extract exerts a protective effect (Figure 3c).<sup>[30]</sup> Withanolide, a compound derived from *W. somnifera*, is often used in ayurvedic medicine to treat OA, and RA. Withanolide shows chondroprotective action by preventing collagenase activity.<sup>[31–33]</sup>

The Chinese herb *Angelica sinensis*, sometimes known as female ginseng, is a member of the Apiaceae family. *A. sinensis* root extract contains the secondary metabolite ligustillide (Figure 3d) that is responsible for the plant's anti-arthritic activity.<sup>[34,35]</sup> Ligustillide reduced the levels of p65, IKK $\alpha$ , and IKK $\beta$ , and decreased the expression of MMP-3, ADAMTS-5, iNOS, and COX-2, according to the results of a series of studies. Also, it suppresses the IL-1 $\beta$  induced degradation of collagen and aggrecan.<sup>[36,37]</sup>

*Glycyrrhiza glabra*, sometimes known as licorice, or mulaithi, is a legume in the family Leguminosae. There are several

traditional uses for *G. glabra*, including treating coughs, colds, and swelling, as well as acting as a diuretic, and pesticide.<sup>[38]</sup> *G. glabra* contains active secondary metabolites like glycyrrhizin, flavonoids, saponoids, sterols, starches, amino acids, gums, Liquiritin, glabridin, glabrene, liquiritigenin, glabrolide, isoglabrolide, liquiritic acid, glypallidifloric acid, glycyrrhetol (glycyrrhetol), liquiridolic acid.<sup>[39,40]</sup> Glycyrrhizin, a chemical extracted from the root of the plant, has also been linked to OA. There are anti-inflammatory and anti-collagen degradation effects of glycyrrhizin (Figure 3e). In addition, studies show that glycyrrhizin protects the chondrocytes in OA.<sup>[41–44]</sup>

*Saposhnikovia divaricate* is a perennial plant from the Umbelliferae family that may be found throughout North Asia. Various active phytochemicals in the dried root of this plant have been used to treat nervous system, immune system, and respiratory diseases. Examples include: isobergaptin, imperatorin, pentacosane acid, anomalin, decursin, 5-methoxy-7-(3,3-dimethylallyl-oxy) coumarin, decursinol angelate, xanthotoxin, bergapten, tectochrysin, scopoletin, hamaudol, ledebouriellol, cimifugin, sec-O-glucosylhamaudol, 4'-O-beta-D-glucosyl-5-O-methylvisamminol, and prim-O-glucosylcimifugin.<sup>[45,46]</sup> For OA, *S. divaricate* is mainly used for inflammation by inhibiting the production of cytokines and also protecting cartilage.<sup>[44,45]</sup>

*Camellia sinensis* is, commonly known as green tea, belongs to the family *Theaceae*. Bioactive chemicals found in tea plants have a significant impact on the cosmetics sector. Bioactive substance Epigallocatechin-3-gallate (Figure 3f) has a potential for the treatment of osteoarthritis (OA).<sup>[47]</sup> Research shows that it inhibits chondrocytes' release of lactate dehydrogenase. So, it may help alleviate the symptoms of osteoarthritis (OA), and its complications.<sup>[48–51]</sup>

*Ribes nigrum*, more often known as blackberries, provide a wide range of beneficial compounds for human health. There are many flavonoids in black berries that are beneficial to health, including rutinoides, pelargonidin, cyanidin, peonidin, delphinidin, prodelfinidins, petunidin, and malvidin, cyanidin 3-O-araboside, delphinidin, anthocyanins, myricetin-3-O-glucoside, flavan-3-ols, hydroxycinnamic acids, myricetin aglycone, gallic acid, epigallocatechin.<sup>[52]</sup> In addition, the leaves extract of *R. nigrum* contains the compound prodelfinidins (Figure 3g), having significant potential. Some trials show that prodelfinidins have an inhibition potential on cyclooxygenase *in-vitro*.<sup>[52,53]</sup>

Sappan wood is the common name for a species of *Caesalpinia sappan*, a member of the Leguminosae family. To treat blood-related diseases including dysmenorrhea, amenorrhea, and pain from external injuries, *C. sappan* is often used in TCM (Traditional Chinese Medicine). Glycosides,  $\beta$ -amyrin, glucose, brazilin, caesalpin J and P and protosappanin A, and

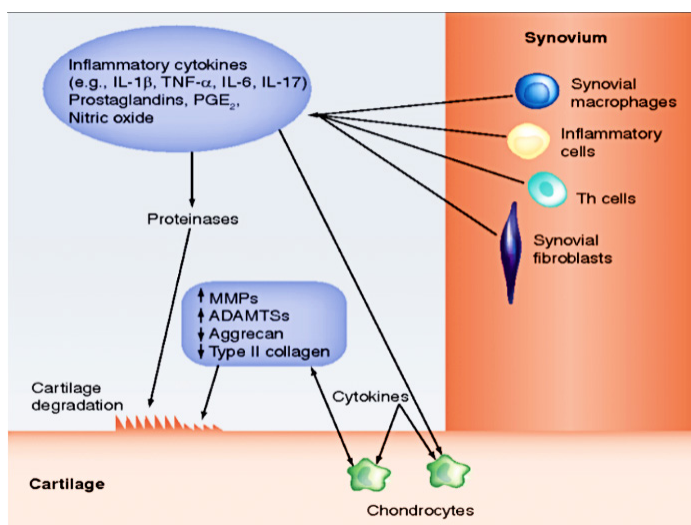


Figure 2: Pathophysiology of OA.

B, homoisoflavonoids  $\beta$ -sitosterol, sappanol, episappanol, quercetin, rhamnnetic and brazilin, and brazilin are some of the phytochemicals found in *C. sappan*.<sup>[54]</sup> Brazilianin (Figure 3h) has been shown to decrease inflammatory cytokines in certain *in vitro* tests, which suggests that an ethanolic extract of the plant might be used to treat arthritis.<sup>[54–56]</sup>

*Pinus pinaster* contains pycnogenol, a US-registered name for a product having anti-inflammatory, and chondroprotective supplements. Pycnogenol is extracted from the *Pinus* plant that belongs to the family Pinaceae. Commonly known as maritime pine and contain various bioactive chemicals like Glycoside,  $\beta$ -amyrin, glucose, brazilin, caesalpin J, caesalpin P, protosappanin A, protosappanin B, homoisoflavonoids  $\beta$ -sitosterol, sappanol, episappanol, quercetin, rhamnnetic, brazilin, brazilin.<sup>[57,58]</sup> However, pycnogenol, which is extracted from plants, has been shown to have chondroprotective effects in cartilage, and to help avoid the pain associated with OA.<sup>[59–61]</sup>

*Betula platyphylla*, a member of the Betulaceae family, has been linked to osteoarthritis. Subarctic and temperate Asia, including Japan, Russia, Korea, and China are home to this species. Proteoglycan breakdown is prevented by inhibiting the expression of MMP-3 and MMP-13.<sup>[62]</sup> Triterpenoids, diarylheptanoids, phenylbutanoids, flavonoids, catechins, and steroids are only a few of the plant's other active phytochemicals.<sup>[63,64]</sup>

*Pongamia pinnata* is a monotypic species belonging to the family Papilionaceae. It is widely distributed and has potential for different diseases, also showing potential for OA. *P. pinnata* contain very effective phytochemicals like Sterols, beta-sitosteryl acetate, galactoside, stigma sterol, galactoside, stearic acid, palmitic acid, Karangin, pongamol, pongagalabrone, pongapin, pinnatin, kanjone, pongol, Glabrachalcone, isopongachromene, Galbone, Pongalabol, pongagallone A.<sup>[65]</sup> According to research, hydroxyproline in the urine and other mediators of collagen, and cartilage breakdown are reduced, as are the lysosomal enzymes

responsible for cartilage destruction. The anti-inflammatory characteristics of *P. pinnata* aid with inflammation discomfort as well.<sup>[65–67]</sup>

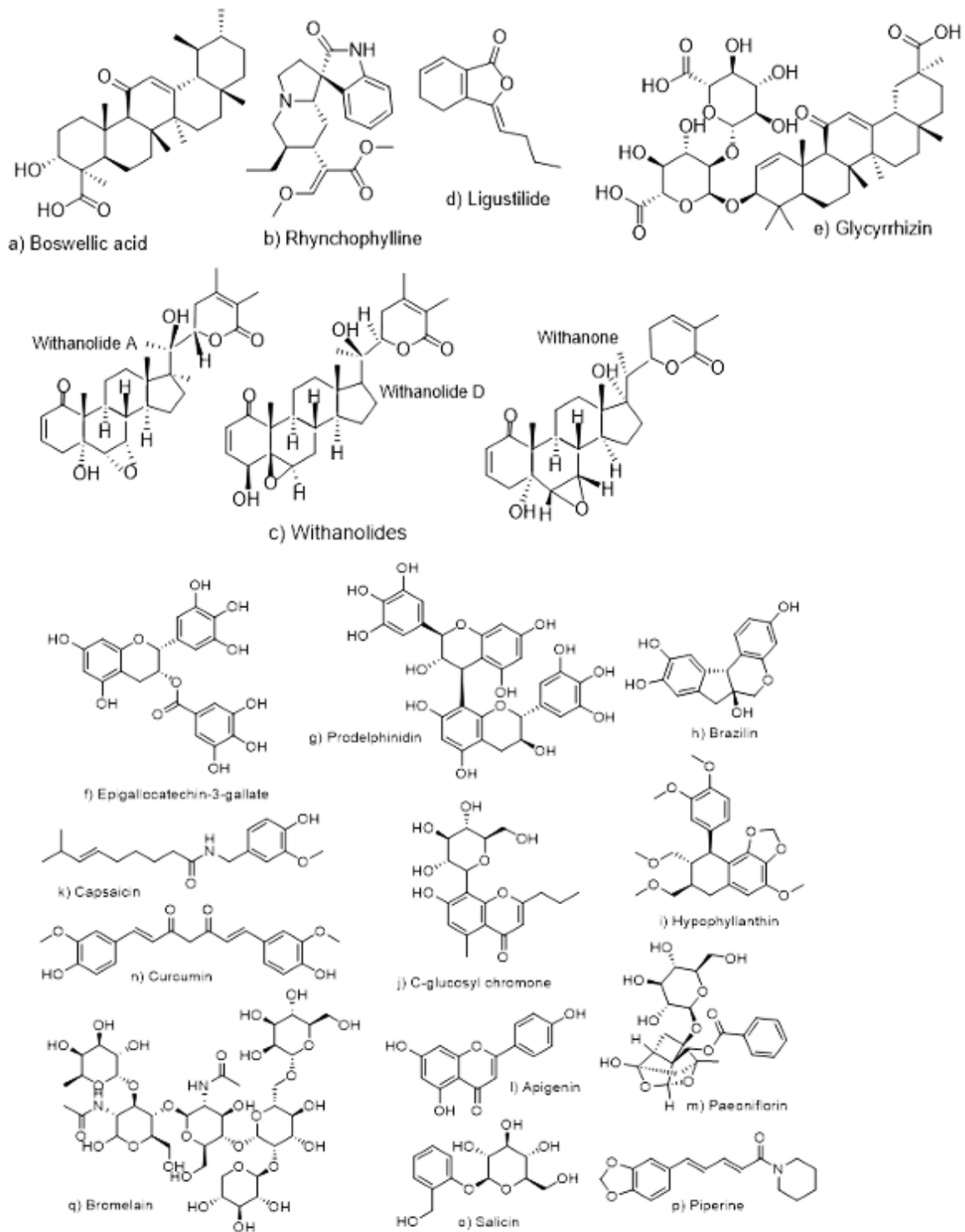
*Commiphora mukul* is commonly known as guggul belonging to the family Burseraceae. It's found in dry regions of India, and gum resin has the potential to treat OA. Guggul contains bioactive compounds like guggulsterol, guggulsterone, flavonoids, and coumaric acids. In OA, guggul prevents the chondrocytes breakdown.<sup>[33,68,69]</sup>

*Phyllanthus amarus* Schum, commonly known as *Bhumi amla*, is a small herb having potent medicinal values, and is used worldwide. In the Indian ayurvedic system, *P. amarus* is reported crucial medicinal plant to treat various diseases associated with the stomach, kidney, liver, spleen, and genitourinary system. The whole plant has a therapeutic value and contains alkaloids (Securinine, nor-securinine, epibubbialine, isobubbialine, dihydrosecurinine), flavonoids, tannins, lignanins, and sterols.<sup>[70]</sup> In addition, it exhibits antiarthritic activity, and is beneficial in OA. Furthermore, some major compounds like phyllanthin, and hypophyllanthin (Figure 3i) show the chondroprotective potential for OA.<sup>[71,72]</sup>

*Aloe barbadensis miller*, common name aloe vera belonging to the family *Asphodelaceae*. Because of its many health benefits, *Aloe vera* has been utilised since antiquity for everything from skin care to wound healing to sunburn relief. *Aloe barbadensis miller* contains secondary metabolites like anthraquinones (aloe-emodin, aloetic-acid, anthranol, barbaloin, isobarbaloin, emodin, ester of cinnamic acid), carbohydrates (acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose), C-glucosyl chromone, and inorganic compounds having potential for different pharmacological activity,<sup>[73,74]</sup> and widely used in the cosmetic industry but it also shows potential for arthritis. C-glucosyl chromone (Figure 3j) is the main component from aloe vera extract showing anti-inflammatory activity and helping in reducing inflammation due to arthritis.<sup>[75,76]</sup>

Capsaicin (Figure 3k) is extracted from plant *Capsicum annum* used topically for OA pain. It is a marketed formulation that directly applies to the skin (topical analgesic). Capsaicin reduces joint pain when rubbed over affected joints.<sup>[25,77]</sup>

The chamomile plant, *Matricaria chamomilla*, is a member of the Asteraceae family. Traditionally, chamomile has been utilised for its therapeutic benefits for thousands of years. Chamomile has the potential for fever, cough, wound healing, and GIT disease.<sup>[78]</sup> Apigenin, luteolin, quercetin, Isobutyl angelate, 2-methylbutyl angelate, farnesene, beta-farnesene, farnesenesol, bisabolol, bisabolol oxide A and B, matricin, Chamazulene, Guaiazulene, and Chamazulene are the primary active components in chamomilla. OA sufferers may benefit from the



**Figure 3:** Phytochemicals having potential against OA.

**Table 1: Plants having potential for treatment of osteoarthritis.**

Biological source and family	Common name	Active chemical	Mode of action	Part used	Solvent used	Reference
<i>Boswellia serrata</i> (Burseraceae)	Salai/Salai guggul	Boswellic acids, Aflapin	Act as a chondroprotective and anti-inflammatory agent	Resin	Organic solvents	[13][33]
<i>Eucommia ulmoides</i> (Eucommiaceae)	Hardy rubber tree	-	Decreases the production of the TNF- $\alpha$ , IL-17, IL-1 $\beta$ , and IL-6 by the reduction of the phosphoinositol 3-kinase (PI3K) signalling pathway activation in OA.	Leaf Bark	Alcohols	[1]
<i>Matricaria chamomilla</i> (Asteraceae)	Chamomile	Apigenin	Inhibit proinflammatory cytokines production, suppress prostaglandin production	Flower	Aqueous ethanol	[80]
<i>Paeonia lactiflora</i> (Paeoniaceae)	Peony, Chandayra, Chandra	Paeoniflorin	Prevent the production of prostaglandins E2, leukotriene B4, nitric oxide	Roots	Aqueous	[66]
<i>Withania somnifera</i> (Solanaceae)	Ashwagandha	Withanolide	Chondroprotective effect	Leaf, root	Aqueous or alcoholic	[29][1]
<i>Zingiber officinale</i> (Zingiberaceae)	Adrak, Ginger	Gingerol	Pain-relief (inhibiting prostaglandin and leukotriene synthesis)	Rhizomes	95% ethanol	[84][85]
<i>Curcuma longa</i> (Zingiberaceae)	Turmeric, Haldi, kurkum	Curcumin	Reduce pain in OA by inhibiting prostaglandins, leukotrienes, and cyclooxygenase-2	Rhizomes	Dichloro methane	[88]
<i>Angelica sinensis</i> (Apiaceae)	Female ginseng	Ligustillide	Stimulate activity of UDP-glycosyltransferase which promote chondroitin synthesis	Root	Ethanol	[34]
<i>Glycyrrhiza glabra</i> (Leguminosae)	Licorice, Sweet Wood, Mulaithi, Mulhathi, Jethimadhu	Glycyrrhizin	Suppress the inflammatory factors and inhibit the COX-2. Also inverted the degradation process of collagen	Root	Hydro-alcohol	[39]

<i>Saposhnikovia divaricate</i> (Umbelliferae)	Radix Saposhnikoviae	-	Protect cartilage and inhibit inflammatory mediators	Root	-	[45][46]
<i>Aloe barbadensis miller</i> (Asphodelaceae)	Aloe vera, Alloeh, Gheekumari	C-glucosyl chromone	Shows strong anti-inflammatory activity and reduces joint pain	Leaves	Methanolic extract	[74][76]
<i>Uncaria tomentosa</i> (Rubiaceae)	Cat's claw	Rhynchophylline, quinovic acid	Inhibit prostaglandin production also effective antioxidant reduce joint pain in osteoarthritis	Stem bark	Hydro-alcohol	[25][28]
<i>Camellia sinensis</i> (Theaceae)	Green tea	epigallocatechin-3-gallate	Inhibits the release of lactate dehydrogenase in human chondrocytes of osteoarthritis cartilage	Leaves	Organic solvents	[47]
<i>Salix daphnoides</i> (Salicaceae)	Willows	Salicin	Effect in treating osteoarthritis joint pain by inhibiting the cyclooxygenase enzyme	Bark	Methanol	[105]
<i>Ribes nigrum</i> (Grossulariaceae)	Blackcurrant	Prodelphinidins	Stimulated synthesis of proteoglycans and type II collagen in chondrocytes	Berries	Acetone	[52]
<i>Justicia gendarussa</i> (Acanthaceae)	Willow-leaved Justicia, Gendarussa vulgaris	-	Anti-inflammatory activity	Leaves	Methanol	[95]
<i>Caesalpinia sappan</i> (Leguminosae)	Sappan Wood,	Brazilin	Reduced the cartilage breakdown in OA	Dried heartwood	Methanolic extracts	[54][55]
<i>Pinus pinaster</i> (Pinaceae)	Maritime pine	Pycnogenol	Chondroprotective effects and inhibition of cartilage-destructing proteases	Bark	Water	[57][58]
<i>Rosa canina</i> (Rosaceae)	Dog rose	$\alpha$ -linolenic acids	Inhibit cyclooxygenase (COX)-1 and COX-2	Fruit, Seed	Organic solvent	[97]

<i>Betula platyphylla</i> (Betulaceae)	Asian white birch, White Birch	–	It inhibits the degradation of proteoglycan and collagen by the downregulation of the MMP-3 and MMP-13 expression	Bark	Methanol extract	[64]
<i>Pongamia pinnata</i> (Papilionaceae)	Karanj	Furano flavonoid	It reduced the collagen and cartilage breakdown markers	Seed	Ethanol	[65]
<i>Commiphora mukul</i> (Burseraceae)	Guggul, guggulu	-	Prevent Chondrocyte damages	Gum resin	Ethanolic	[68]
<i>Phyllanthus amarus</i> Schum (Euphorbiaceae)	Bhumi amla, Jangliamli, Hurricane weed, Shatter stone, Stone breaker	Hypophyllanthi	Chondroprotective effect	Whole plant	Methanol	[71]
<i>Piper longum</i> Linn. (Piperaceae)	Long pepper, Pippali	Piperine	Decreased the IL-1 $\beta$ -stimulated gene expression and also the production of MMP-3, MMP-13, iNOS, and COX-2 in human OA chondrocytes.	Fruit	Chloroform	[101]
<i>Saussurea lappa</i> Clarke (Asteraceae)	Kushta, Indian Costus tree	-	Reduce OA-induced secretion of interleukin-6, TNF- $\alpha$ , and IL-1 $\beta$	Root	Aqueous	[102]
<i>Sesamum indicum</i> (Pedaliaceae)	Sesame, tila	Sesamin, Sesamol, Sesamolol	Reduce pain by inhibiting the oxidative aggression (decline in the peroxidation of lipids and the production of superoxide anion)	Seed	Ethanol	[106][53]
<i>Capsicum annuum</i> (Solanaceae)	Chilli Pepper, Christmas Pepper, Red Pepper, Ornamental Chilli Pepper	Capsaicin	Relieve joint pain from osteoarthritis	Fruit	n-hexane	[25]
<i>Ananas comosus</i> (Bromeliaceae)	Pineapple	Bromelain	Anti-inflammatory action by decreasing levels of PGE2, thromboxane A2	Fruits	Ethanol	[109]
<i>Arnica montana</i> (Asteraceae)	Leopard's bane	-	Reduces pain	Flowers	Hydro-alcohol	[111][112]



<i>Rosmarinus officinalis</i> (Lamiaceae)	Rosemary	-	Reduces pain and improves physical function in knee osteoarthritis patients	Leaves	Organic solvents	[114]
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usage of chamomile in their treatment regimens as well. The use of analgesics by individuals with osteoarthritis of the knee has been shown to be reduced when chamomile oil was administered. Chamomile's apigenin (Figure 3l) has also been shown to have anti-OA properties. Cytokine production and MMP-3 expression are reduced by Apigenin.<sup>[79,80]</sup>

Decoction of the roots of *Paeonia lactiflora*, which are members of the family Paeoniaceae, and are used to treat inflammatory illness. Peony, chandayra, and Chandra are all frequent names for this flower. Water and ethanolic extract of these plants contain the active compound, i.e., Paeoniflorin (Figure 3m), showing activity for OA. Paeoniflorin in preclinical studies showed activity like alleviating pain, bone erosion, joint swelling, and cartilage degradation in experimental animals. In addition, it reduces pain by inhibiting prostaglandins, and proinflammatory cytokines.<sup>[81-83]</sup>

*Zingiber officinale* belonging to the family Zingiberaceae, is commonly known as ginger, and ginger extract has potential for RA. Moreover, its extract has a moderate effect on OA patients by reducing the pain symptoms of OA.<sup>[84,85]</sup> Mainly in OA, it inhibits the inflammatory mediators, which shows a decrease in pain, and inflammation in OA patients.<sup>[86,87]</sup> Even, *Curcuma longa* belonging to the same family Zingiberaceae, commonly known as turmeric, or haldi, has many pharmacological activities. It is used for a variety of ailments like cancer, neuroprotective, anti-inflammatory, anti-apoptotic, and also used as anti-bacterial due to active phytochemicals like curcumin, demethoxycurcumin, bisdemethoxycurcumin, turmerone, santalene, santalenone,  $\beta$ -sesquiphellandrene terpinolene, curcumenol, curdione, curcumol.<sup>[88]</sup> Turmeric's curcumin (Figure 3n) has been shown in tests to be useful in treating OA.<sup>[89]</sup> Curcumin inhibits the inflammatory process by reducing the cyclooxygenase enzyme activity and reducing interleukins. Therefore, it is suggested that curcumin, or its supplements improve OA condition when used for more than 12 weeks.<sup>[90-93]</sup>

*Justicia gendarussa* is a quick growing and evergreen plant belonging to the family Acanthaceae. It is primarily grown in the moist area and widely cultivated in India and Malaysia. It contains an alkaloid, steroid, flavonoid, phenol, carbohydrate, saponin, and quinone stigmaterol, lupeol,  $\beta$ -sito-sterol, and J. gendarussa used in many diseases from ancient times like used to treat respiratory illness, fever, arthritis, and also used in muscle pain.<sup>[94]</sup> The plant's ethanolic extract has been shown in recent research to have the ability to cure OA. The MMP-9 and iNOS enzymes are both inhibited by the *J. gendarussa* extract, which

reduces inflammation. In order to manage OA pain, it is most often utilised.<sup>[95,96]</sup>

Dog rose, also known as *Rosa canina*, is a traditional remedy for a variety of ailments.<sup>[97]</sup> Flavonoids (anthocyanins, flavones, flavanols, isoflavones, flavanols, flavanones), carotenoids (lutein, zeaxanthin, and cryptoxanthin, alpha-carotene, beta-carotene, and lycopene), fatty acids (-linolenic acids), vitamins, and triterpenes have all been extracted from the plant. By suppressing the inflammatory mediators and COX enzyme, the *R. canina* is utilised to treat osteoarthritis. It is mainly used for the pain associated with osteoarthritis pain.<sup>[98]</sup>

Piperine (Figure 3p) isolated from *Piper longum* Linn., family Piperaceae is a phenolic compound having the potential for OA. Piperine inhibits the MMP-13 and prostaglandin production in chondrocytes. In rat models, piperine reduces arthritis symptoms, and pain sensation due to OA.<sup>[99-101]</sup>

*Saussurea lappa* clarke, commonly known as kushta has many therapeutic applications. It contains many active compounds like sesquiterpenes, sulfocostunolide A, sulfocostunolide B, saussureamine B, saussureamine C, arbusculin A,  $\beta$ -costic acid, santamarin, reynosin,  $\alpha$ -amyrin,  $\alpha$ -amyrin stearate, pregnenolone, and lappasterol.<sup>[46,102]</sup> Preclinical studies showed that *Saussurea lappa* has anti-osteoarthritic activity by inhibiting the MMP expression and NF- $\kappa$ B signalling pathway in the mice model.<sup>[103,104]</sup>

*Salix daphnoides* known as willow bark is traditionally used for articular pain. Willow bark aqueous and hydroalcoholic extract contain active phytochemical salicin (Figure 3o). Salicin inhibits the cyclooxygenase enzyme and reduces osteoarthritis pain.<sup>[93,105]</sup>

Indicated sesame *Sesamum indicum* commonly known as tila, a member of the Pedaliaceae family, yields sesame oil. Sesame oil is a traditional medicine used as an antioxidant, anti-inflammatory, anti-bacterial, and it contains phytochemicals like unsaturated fatty acids, oleic acid, palmitic acid, tocopherols,  $\gamma$ -tocopherol,  $\beta$ -sitosterol,  $\alpha$ -,  $\gamma$ - and  $\delta$ -tocopherols,  $\delta$ -tocopherol, sesamin, sesamol, sesamol.<sup>[53,106]</sup> According to recent research, sesame oil may alleviate the pain, and stiffness associated with osteoarthritis of the knee.<sup>[107,108]</sup>

The fruit *Ananas comosus*, which contains the antioxidant bromelain, may be used to treat OA.<sup>[109]</sup> Pineapple (*A. comosus*) is a member of the Bromeliaceae family and its stem has a greater concentration of bromelain. Anti-inflammatory, anti-edematous, and antithrombotic properties of bromelain have been reported.

However, more studies are needed to investigate the bromelain (Figure 3q) in OA treatment.<sup>[67,110]</sup>

Known as the leopard plant, *Arnica montana* is a member of the Asteraceae family, and its gel is used to treat OA pain. Its gel reduces pain and stiffness in OA patients when applied twice daily for three weeks. *A. montana* also improve physical functions of OA patients.<sup>[111–113]</sup>

Traditionally, the herb rosemary, scientifically known as *Rosmarinus officinalis*, has been used to treat conditions including asthma, dysmenorrhea, and the discomfort associated with renal colic. Anti-inflammatory, antioxidant, and anti-nociceptive benefits are all attributed to Rosemary. Monoterpenes are the primary constituents of rosemary. *In-vitro* studies of rosemary reveal that its extract slows down the cartilage degeneration process and could be used for the treatment of OA. Also, the emulsion of peppermint essential oil and rosemary reduces OA joint pain, and improve histopathological features of rat joint.<sup>[114,115]</sup>

## CONCLUSION

Herbal drugs and their bioactive fractions are probably valuable for preventing or alleviating the pain and progression of OA. A variety of civilizations across the world make use of herbal treatments for treating OA. Many herbal remedies have been developed as a result of research into the anti-osteoarthritic properties of herbal plants. A variety of data were obtained for this study, including information on the plant's potential, toxicity profile, mechanism of action, and the phytochemical responsible for anti-osteoarthritic efficacy. Finally, we can say that several of the plants included in Table 1 exhibit anti-osteoarthritic action that is promising. Inflammatory mediators are reduced in people with rheumatoid arthritis by certain plants, while others stop the destruction of cartilage.

## ACKNOWLEDGEMENT

The authors thanks the management of Maharishi Markandeshwar (Deemed to be University), Mullana, Ambala, Haryana for this review.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## Limitations and Future prospective

Several plants are reported which could be utilised in the treatment of OA as mentioned in the Table 1, but some traditional plants used in OA treatment are not experimentally proven in the OA treatment. Some plants showed anti-arthritis activity in the preclinical stage, but the clinical data is not available for those plants. Also, data for the active isolated phytochemical is not adequately available for the OA. Most of the plants used in OA

reduce NSAID usage, i.e., reduce the inflammatory mediators and reduce pain associated with the OA, but then again do not work on the chondrocytes, or cartilage degradation. So, further research, and clinical trials are needed to determine the anti-osteoarthritic activity of less explored plants.

Several clinical studies showed the target is cartilage lesions with reduced pain and inflammation, but there are very few plants showing the improvement in cartilage. However, there are significantly fewer herbal or allopathic drugs that reverse, or stop osteoarthritis's progression in the long term. So, the primary future approach for osteoarthritis treatment is must be focused on regenerative, or pharmacological therapy for the joint. So, the modulation of the mechanoreceptive pathway is the foremost new opportunity for osteoarthritis study. Also, exploration of new herbal plants, and clinical studies are required for osteoarthritis treatment.

## ABBREVIATIONS

**ADAMTS-5:** ADAM Metalloproteinase with Thrombospondin Type 1 Motif 5; **IL-1:** Interleukin-1; **iNOS:** Inducible nitric oxide synthase; **MMPs:** Matrix metalloproteinases; **NF  $\kappa$ B:** Nuclear factor kappa B; **NO:** Nitric oxide; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **OA:** Osteoarthritis; **PGE2:** Prostaglandin E<sub>2</sub>; **RA:** Rheumatoid arthritis; **TNF:** Tumour necrosis factor; **UTI:** Urinary tract infection.

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