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REVIEW ARTICLE

Translating Tradition into Therapy: Evidence-based Medicinal Plants for the Modulation of Osteoarthritis Biomarkers

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Abstract

A chronic and degenerative joint condition, Osteoarthritis (OA) causes the subchondral bone to shift structurally, articular cartilage to gradually deteriorate, and inflammation to persist. OA is currently one of the main causes of disability, especially in the elderly, affecting over 595 million people globally. There is a need for safer and more sustainable alternatives because conventional treatment, which usually relies on analgesics and Nonsteroidal Anti-Inflammatory medicines (NSAIDs), is mostly palliative and frequently linked with adverse effects. Medicinal herbs have been used for centuries to treat joint-related conditions in traditional medical systems, such as *Ayurveda*, Traditional Chinese Medicine (TCM), and ethnomedicine. The medicinal benefits of these herbs, many of which have anti-inflammatory, antioxidant, and cartilage-protective properties, are now being confirmed by recent scientific studies. They work by modifying key molecular pathways, including NF-κB, MAPK, JAK/STAT, MMP, AMPK, and LOX. This review explores the pathophysiology of OA and provides a thorough evaluation of some of the herbal and polyherbal remedies that have been investigated in experimental OA models. The phytoconstituents such as curcumin, quercetin, kaempferol, and boswellic acids demonstrate significant potential in attenuating disease progression. Integrating traditional botanical therapies with modern treatment strategies could offer a more holistic and multi-targeted approach to OA management. Ultimately, bridging traditional practices with scientific rigour may help advance safer, effective, and affordable interventions for patients living with osteoarthritis.

Major Findings: Medicinal plants traditionally used in *Ayurveda* and TCM show strong anti-inflammatory, antioxidant, and cartilage-protective effects by modulating key OA-related pathways such as NF-κB, MAPK, and MMPs. Plants like *Balsamodendron mukul, Boswellia serrate, Curcuma longa* and *Zingiber officinale roscoe* exhibit significant potential in reducing osteoarthritis progression, offering safer and multi-targeted therapeutic alternatives.

Keywords: Anti-Inflammatory, Cartilage Protection, Herbal Plants, NF-κB Pathway, Osteoarthritis, Phytoconstituents

Abbreviation:OA- Osteoarthritis; NF-κB- Nuclear Factor kappa-light-chain-enhancer of activated B cells; MAPK- Mitogen-Activated Protein Kinase; JAK/STAT- Janus Kinase / Signal Transducer and Activator of Transcription; MMP- Matrix Metalloproteinase; AMPK- Adenosine Monophosphate-Activated Protein Kinase; LOX- Lipoxygenase; TIMPs- Tissue Inhibitors of Metalloproteinases. KOA-knee osteoarthritis; HIF-1α- Hypoxia-Inducible Factor 1-alpha; iNOS- inducible Nitric Oxide Synthase; SOD- Superoxide Dismutase; CAT- Catalase; AGN- Andrographolide; FLSs- Fibroblast-like Synoviocytes; FJH-KO- Fermented Jellyfish Hydrolysate–Knee Osteoarthritis; HMGB1- High Mobility Group Box 1; TLR4- Toll-Like Receptor 4; TMJ- Temporomandibular Joint.

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1. Introduction

Osteoarthritis (OA) is a widespread joint disorder defined by the slow deterioration of the protective cartilage that gives bones their ends. This deterioration causes pain, stiffness, and restricted mobility. It can affect the hands and other areas, although it primarily affects weight-bearing joints like the knees, hips, and spine and is a leading cause of disability in the elderly population[1]. In 2020, osteoarthritis affected 595 million people (7.6% of the global population), a 132.2% rise since 1990. By 2050, cases are expected to increase significantly: knee (74.9%), hand (48.6%), hip (78.6%), and other types (95.1%). The age-standardised Years Lived with Disability (YLD) rate was 255 per 100,000 in 2020, up 9.5% since 1990, with osteoarthritis ranking as the 7th leading cause of YLDs in those aged 70 and above[2].

The exact cause of osteoarthritis remains unclear. Primary osteoarthritis typically develops gradually with ageing, as natural joint wear contributes to cartilage deterioration. Additionally, direct joint injuries, such as those from sports activities, falls, or car accidents, can lead to the condition. Certain medical conditions, including Ehlers-Danlos syndrome and joint hypermobility syndrome, may also increase the risk of osteoarthritis. Furthermore, other forms of arthritis, particularly inflammatory types such as rheumatoid arthritis, gout, and psoriatic arthritis, can contribute to its development[3]. Treatment focuses on pain relief and improving joint function. Treatment primarily aims to reduce pain and improve joint function. NSAIDs, including ibuprofen, naproxen, and diclofenac, are first-line therapies due to their ability to reduce both pain and inflammation. However, they may cause gastrointestinal irritation, kidney damage, and increased blood pressure. When NSAIDs are contraindicated, analgesics like acetaminophen (paracetamol) are used to relieve pain, though they lack anti-inflammatory effects and carry risks such as liver toxicity, nausea, and allergic reactions[4,5].

In traditional medicine systems such as *Ayurveda*, Traditional Chinese Medicine (TCM), and ethnomedicine, numerous plants have been used to alleviate symptoms associated with OA. These herbs exert anti-inflammatory, antioxidant, and cartilage-preserving effects through various biochemical pathways. Scientific validation of these traditional remedies is essential to bridge the gap between historical use and evidence-based therapy.

Concerns regarding the safety and costs of conventional osteoarthritis therapies have sparked interest in natural remedies. In addition, difficulty with chronic pain management in OA has led to the investigation of herbal therapies. Herbs may offer an alternative method for effective and safe treatment. In this review, we summarise the experimental findings related to 50 plant species and their bioactive constituents, experimental models, and mechanisms of action involved in OA attenuation. The focus is placed on their ability to modulate key inflammatory and degradative pathways implicated in OA pathogenesis. Specifically, we also provide descriptions of individual herbal medicinal plants used for OA.

2. Pathophysiology

Figure 1 shows that the central feature of OA is the interplay between oxidative stress, chronic inflammation, and cellular dysfunction within the joint microenvironment. The process begins with increased oxidative stress and chronic inflammation, which recruit inflammatory cells such as macrophages and neutrophils to the joint space. These cells secrete proinflammatory cytokines, primarily Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and Tumour Necrosis Factor-alpha (TNF-α), which amplify inflammation and promote further cellular damage. These cytokines activate chondrocytes, the resident cartilage cells, triggering them to produce Matrix Metalloproteinases (MMPs), enzymes that degrade cartilage extracellular matrix components like aggrecans and type II collagen. This degradation weakens the structural integrity of the cartilage. Simultaneously, the bone remodelling balance is disrupted. The number of osteocytes (mature bone cells) and osteoblasts (bone-forming cells) is reduced, leading to bone surface invaginations and increased bone fragility. These skeletal changes contribute to subchondral bone remodelling, worsening joint function. The cumulative result of these molecular and cellular events is cartilage stiffness and degradation, which compromises joint cushioning and mobility. This ultimately manifests clinically as osteoarthritis, characterised by joint pain, stiffness, and functional impairment[6,7].

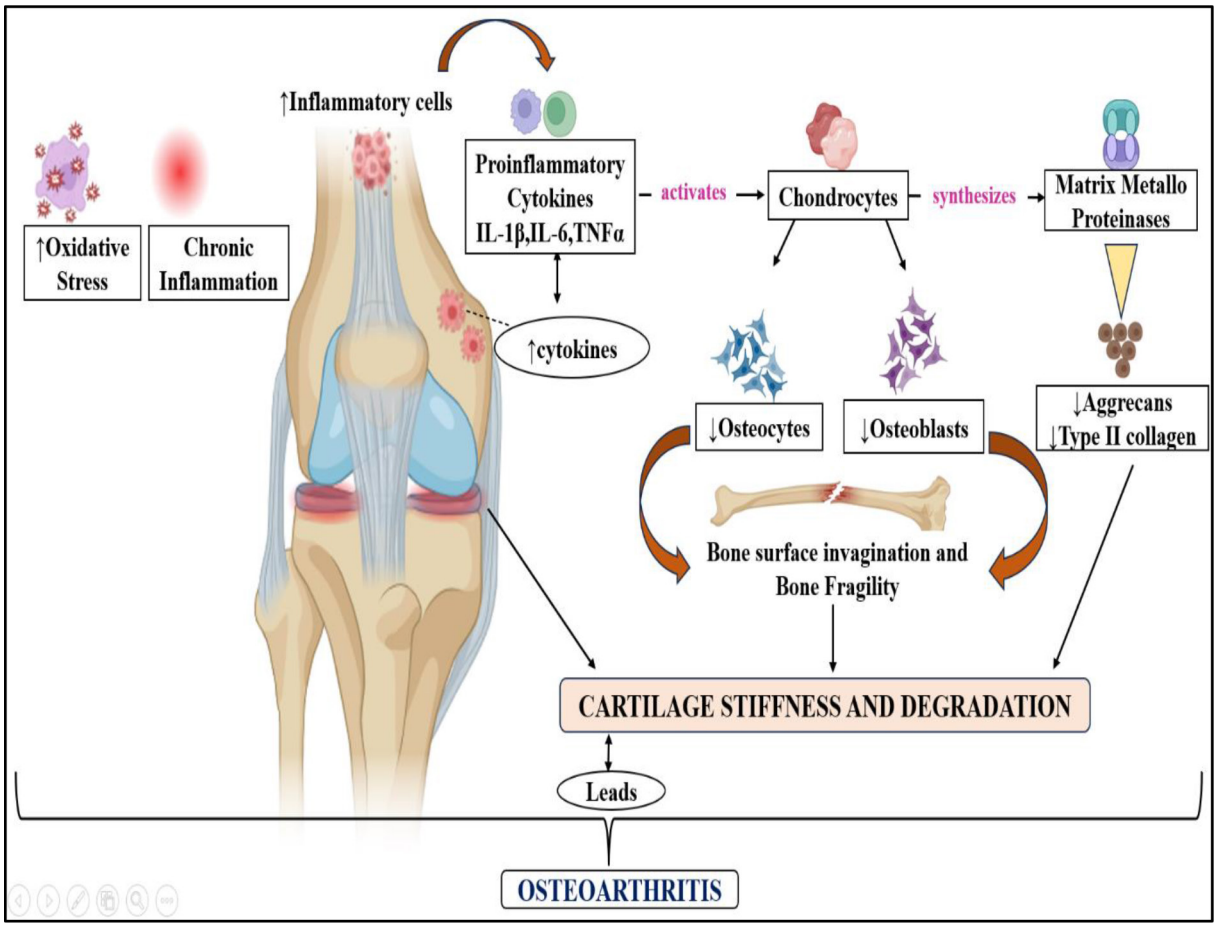


Figure 1. Pathophysiology of OA.

2.1 Signalling Pathway Involved in OA

2.1.1 NF-κB Signalling Pathway

The NF-κB pathway plays a central role in driving inflammation and tissue damage in OA[8]. Under normal conditions, it stays inactive in the cytoplasm, where NF-κB proteins like p50 and p65 are bound to the inhibitory protein IκB. However, when joint cells are exposed to stressors such as inflammatory cytokines, mechanical stress, UV light, or microbial toxins, the IKK complex (IKKα, IKKβ, and IKKγ) is activated[9]. Using ATP, this complex phosphorylates IκB, marking it for degradation. This process frees NF-κB proteins, allowing them to move into the nucleus and activate genes responsible for inflammation, pain, and cartilage breakdown. In OA, this pathway is chronically active, leading to ongoing production of inflammatory mediators and enzymes like MMPs, which further damage cartilage as shown in Figure 2. Due to its key role in disease progression, the NF-κB pathway is being studied as a promising therapeutic target to reduce inflammation and slow joint deterioration in OA[10].

2.1.2 MMP Signalling Pathway

Matrix metalloproteinases (MMPs) are a group of enzymes that normally help maintain and remodel joint tissue. But in OA, these enzymes go into overdrive. Instead of just clearing out old or damaged components, they start breaking down the cartilage that cushions the joints, especially the type II collagen that gives cartilage its strength and structure. This destructive process doesn't happen on its own. It's fueled by chronic inflammation[11]. Inflammatory messengers like IL-1β and TNF-α produced by stressed cells within the joint stimulate an increase in MMP production. The most damaging of these is MMP-13, which aggressively targets type II collagen. MMP-1 and MMP-8 also break down collagen, while MMP-3 helps activate other MMPs, amplifying the damage. Normally,

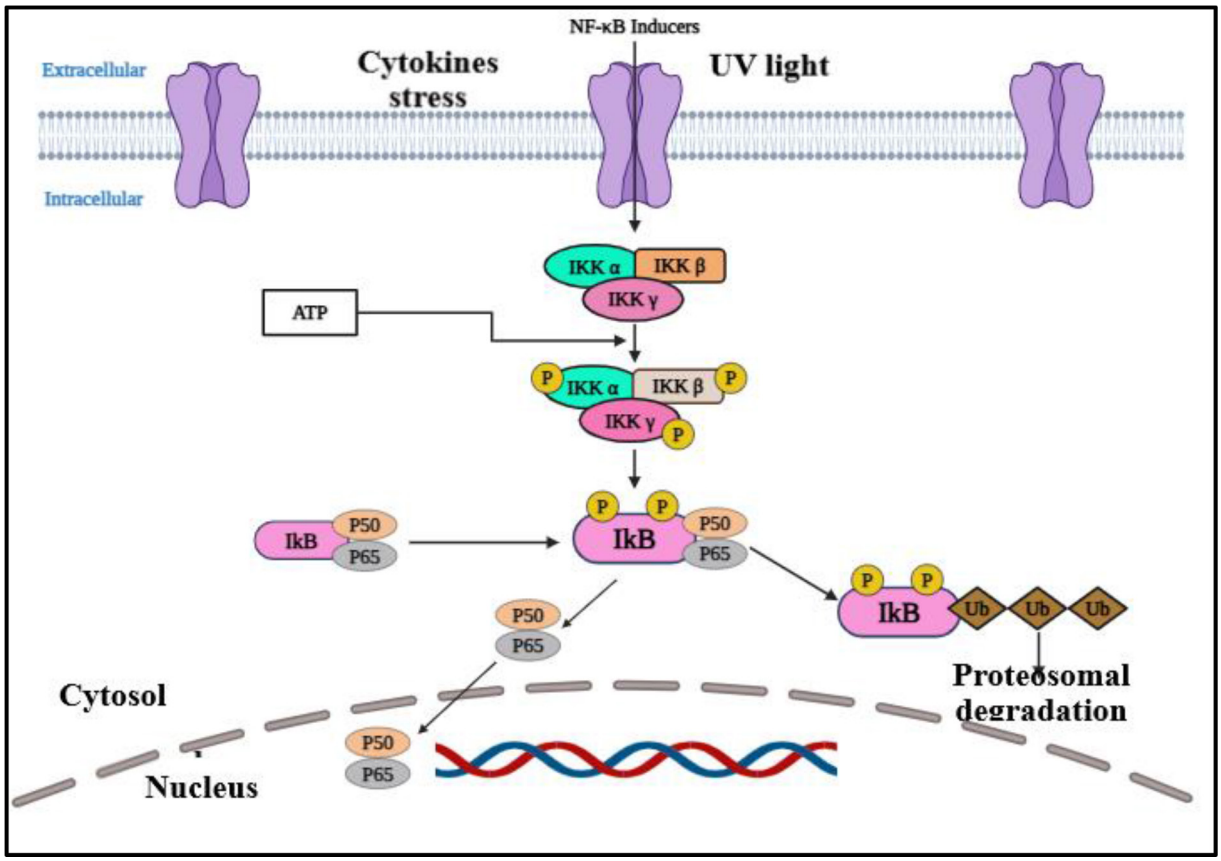


Figure 2. The NF-κB pathway is involved in OA.

the body keeps MMP activity in check with natural inhibitors called TIMPs. But in OA, this balance is lost. TIMP levels drop or become less effective, and MMPs dominate. As a result, the joint's protective cartilage deteriorates, the underlying bone becomes exposed, and inflammation worsens, leading to pain and stiffness typical of OA. Because of their central role in joint damage, MMPs have become an important target for new OA treatments. Researchers are now exploring various ways to block MMPs, including synthetic drugs that interfere with their zinc-based active sites. The hope is that by reining in MMPs, we can slow or even halt the progression of osteoarthritis[12,13].

2.1.3 MAPK Signalling Pathway

The MAP kinase pathway plays a crucial role in the progression of osteoarthritis by regulating inflammation, cartilage degradation, and joint pain. This signalling network includes ERK (Extracellular signal-Regulated Kinase), JNK (c-Jun N-terminal Kinase), and p38 kinases, which are activated by stress signals such as cytokines and matrix fragments. Once triggered, they promote the expression of matrix-degrading enzymes like MMPs, which break down cartilage. OA cartilage and synovium have been shown to exhibit elevated MAPK activity, which connects these pathways to injury to joint tissue. Although preclinical models have demonstrated promise in lowering cartilage degradation and discomfort by the inhibition of MAPKs, particularly JNK and p38, their wide range of cell functions raises safety concerns for clinical application. All things considered, MAP kinases are attractive therapeutic targets in OA, and if safety concerns are resolved, they may be able to alter the progression of the disease and reduce symptoms[14-16].

2.1.4 LOX Signalling Pathway

The 5-lipoxygenase (5-LOX) pathway plays a notable role in OA by generating bioactive lipid mediators called leukotrienes. Leukotriene B4 (LTB4), a powerful chemotactic agent that attracts immune cells to the joint region, is produced when 5-LOX metabolises arachidonic acid in response to cellular stress or inflammatory stimulation. Local inflammation

increases due to the influx of inflammatory cells, which leads to cartilage degradation, irritation of the synovial membrane, and chronic joint discomfort. Research has shown that OA cartilage and synovial fluid had elevated 5-LOX expression and elevated LTB4 concentrations, indicating the pathway's active role in disease processes. Leukotrienes have been studied less than prostaglandins in OA, although there is considerable evidence that they play a significant role in maintaining chronic inflammation. Therapeutically, inhibiting 5-LOX activity or blocking leukotriene receptors may offer promising avenues to dampen inflammation and potentially slow OA progression[17-19].

2.1.5 AMPK Signalling Pathway

AMPK is an enzyme crucial for maintaining cellular energy balance. It has three parts: one catalytic subunit (α) and two regulatory subunits (β and γ)[20]. AMPK is activated when energy levels are low by phosphorylation at Thr-172, primarily by LKB1 (Liver Kinase B1) and CaMKK2 (Calcium/Calmodulin-Dependent Protein Kinase Kinase 2) enzymes. In healthy joints, AMPK is active, but its activation is reduced in OA patients. Reduced AMPK activity in OA may be linked to decreased LKB1 activity. CaMKK2 is increased in OA cartilage, but its role in AMPK activation is unclear. Lower AMPK activity in OA may lead to more severe joint damage, suggesting AMPK is protective for cartilage. Transforming Growth Factor-β–Activated Kinase 1 (TAK1) is an enzyme that can potentially activate AMPK in certain cell types *in vitro*. Overexpressing TAK1 in rats led to cartilage damage while inhibiting TAK1 protection against cartilage degradation in an OA model. The study did not explore whether TAK1 directly activates AMPK in cartilage, so the link between TAK1 and AMPK activation *in vivo* remains unclear. Mitochondrial dysfunction in OA chondrocytes is associated with abnormal AMPK activity, suggesting the role of AMPK in OA development[21,22].

2.1.6 JAK/STAT Signalling Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway plays a pivotal role in the pathogenesis of OA[23]. Activated by pro-inflammatory cytokines like IL-6, IL-1β, and TNF-α, this pathway mediates the downstream transcription of genes involved in inflammation, cartilage degradation, and apoptosis. In chondrocytes, IL-6 binds to its receptor and activates JAKs, which phosphorylate STAT proteins primarily STAT3. The STAT3 dimers translocate into the nucleus, promoting the expression of matrix-degrading enzymes such as MMP-13 and ADAMTS, contributing to Extracellular Matrix (ECM) breakdown and joint destruction[24]. Moreover, JAK/STAT signalling is implicated in immune cell polarisation within the synovial membrane, especially in skewing macrophage populations toward the pro-inflammatory M1 phenotype. Conversely, STAT6 activation supports the anti-inflammatory M2 phenotype, offering potential for therapeutic modulation. Persistent JAK/STAT activation disrupts cartilage homeostasis and amplifies disease progression, positioning this pathway as a promising target for disease-modifying OA therapies[25,26].

3. Medicinal Plants and their Anti-osteoarthritis Actions

The main goal of this review is to gather information about promising active phytochemicals from medicinal plants that have been studied in osteoarthritis models. Table 1 shows medicinal plants and their animal model and pathway, which reveals potential as an anti-osteoarthritis activity.

4. Description for Plant

4.1 *Agnuside alleviates* (*Verbenaceae*)

Agnuside alleviates (*Verbenaceae*) has been claimed as a powerful remedy for arthritis. An experiment employing MIA-induced KOA model rats will chemically examine the effects of oral gavage-delivered AGN on oxidative stress, NLRP3 inflammasome activation, synovitis, and fibrosis in KOA. Treatment with AGN in synovial fluid (FLSs) resulted in lower HIF-1α levels and important NLRP3 inflammasome activation components. AGN also reduced levels of proinflammatory cytokines IL-1β and IL-18 in the FLS culture supernatant. The study demonstrates that AGN attenuates synovitis and fibrosis in the experimental KOA model by inhibiting HIF-1α accumulation and NLRP3 inflammasome activation[27,28].

Table 1. Herbal intervention for the management of osteoarthritis

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
1	*Agnuside alleviates*	Extract of *Vitex negundo* L.	Agnuside, quercetin, kaempferol, rosmarinic acid,	Male Sprague–Dawley (SD) rats/MIA	NF-κB, MAPK	*A. alleviates* may be used to treat KOA by reducing synovitis and fibrosis by specifically targeting the HIF-1α/NLRP3 axis, leading to a drop in inflammatory molecules like IL-1β and IL-18, as well as factors involved in tissue scarring-ultimately offering both anti-inflammatory and antifibrotic benefits.	27,28
2	*Angelica gigas nakai*	Dried herb/ aqueous extract	Angelol A, angelol B, isoangelol A, polysaccharides, β-sitosterol, luteolin, apigenin, coumarins	Male SD rats/ MIA	NF-κB, MMP	*Angelica gigas Nakai* helps ease osteoarthritis symptoms by calming key inflammation pathways. It inhibits the NF-κB pathway, which causes joint inflammation, and reduces dangerous cytokines, including TNF-α and IL-1β. Additionally, by lowering enzymes like iNOS and COX-2, this activity lessens pain and preserves cartilage.	29-31
3	*Euphausia superba*	Antarctic krill oil	Omega-3 fatty acids, phospholipids, astaxanthin	Male SD rats/ MIA	NF-κB pathway, COX and LOX, MAPK	By suppressing important immunological signals, Antarctic krill oil reduces joint inflammation in osteoarthritis. It decreases the generation of toxic cytokines like TNF-α and IL-1β by blocking the NF-κB pathway. Additionally, this slows down the deterioration of cartilage, protecting joints and providing natural pain relief.	31-34
4	*Aucklandia lappa*	Root/aqueous extract	Costunolide, dehydrocostus lactone, dihydrocostunolide, costuslactone, α-costol, saussurea lactone, and costuslactone	Male SD rats / MIA	IL-1β, IL-6, iNOS	By inhibiting the two main inflammatory pathways, NF-κB and MAPK, *A. lappa* helps reduce osteoarthritis. It affects enzymes that harm joint tissue as well as important inflammatory messengers like TNF-α and IL-1β. It naturally reduces pain and protects cartilage by inhibiting these signals.	35-38
5	*Balsa modendron Mukul* (BDM)	BDM gum resin extract into wheat flour	Polyphenolic compounds, guggulsterones	Male albino Wistar rats/ Papain solution	NF-κB, MMP, COX-2, and 5-LOX	*B. mukul* gum, commonly known as guggul, helps reduce joint inflammation in osteoarthritis by calming the NF-κB pathway. It lowers harmful cytokines like TNF-α and IL-1β while also easing oxidative stress. This combined action protects cartilage, reduces swelling, and supports better joint movement.	37-39

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
6	*Boswellia serrate*	Physical mixture of rhein and boswellic acid	β-boswellic acid, 11-keto-β-boswellic acid (KBA), acetyl-11-keto-β-boswellic acid (AKBA)	Male Wistar rats/Intra-articular injection of collagenase	5-LOX, MMP, NF-κB	By reducing inflammation at its source, boswellic acid aids in the relief of osteoarthritis. It reduces important cytokines that induce joint swelling and injury, such as TNF-α and IL-1β, by blocking the NF-κB pathway. Additionally, by reducing oxidative stress and protecting cartilage, this action naturally supports joint health.	40,41
7	*Crataegus Sinica*	Powdered fruits/ methanolic extract	Quercetin, Rutin, vitexin, and hyperoside, Chlorogenic acid, Caffeic acid, Oligomeric proanthocyanidins, ursolic acid, oleanolic acid, essential oil	Male Wistar rats/MIA	NF-κB Pathway, MMP, COX, and LOX Pathways	By reducing important immune responses, *C. sinica* helps reduce joint inflammation in osteoarthritis. It inhibits the enzymes that cause pain and swelling and reduces inflammatory cytokines like TNF-α and IL-1β. Over time, this natural extract also lessens joint deterioration and preserves cartilage.	42,43
8	*Curcuma longa* L.	Curcumin nanoparticles	Curcumin, demethoxycurcumin, bisdemethoxycurcumin, turmerone, zingiberene, atlone, curlone, ferulic acid, vanillic acid, turmeric	C57BL/6 male mice/Medial meniscotibial ligament (MMTL)	NF-κB, MMP, COX-2, and LOX	By reducing inflammation and inhibiting damaging enzymes in joints, curcumin, particularly in nanoparticle form, helps preserve cartilage. It targets inflammation in the footpads to lower discomfort and important inflammatory signals, including TNF-α and IL-1β. Because of this, it's a natural, multi-purpose way to slow down osteoarthritis and enhance joint health.	44-48
9	*D. asperoides* and *Patersonia umbrosa*	Dried root/ ethanolic extract	Saponins, Quercetin, Kaempferol, Aucubin, Phenolic Compounds	SD rats/MIA	NF-κB, COX-2, and 5-LOX	By inhibiting important signals like IL-1β, TNF-α, and COX-2, the herbal extracts from *Dipsacus asperoides* and *Phlomis umbrosa* help reduce joint inflammation. Additionally, they shield cartilage by inhibiting the NF-κB pathway and lowering toxic enzymes. When combined, they reduce damage and swelling, providing a natural approach to osteoarthritis management.	49-52

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
10	*Dashmoolarishta*	Formulation	Aegle marmelos (Bael), Acacia catechu (Khair), Solanum surattense (surajmukhi), Tribulus terrestris, Sida cordifolia (Bala), Asteracantha longifolia (Talmakhana), Rubia cordifolia (Manjistha)	Swiss albino mice of either sex/MIA	NF-κB	By reducing important inflammatory signals like IL-6 and TNF-α that lead to joint pain and cartilage degradation, *Dashamoolarishta* helps alleviate osteoarthritis. Additionally, it suppresses the NF-κB pathway, which causes inflammation, and prevents enzymes like COX-2 and iNOS. All in all, it naturally reduces OA joint deterioration and oedema.	50, 53,54
11	*Echinacea purpurea*	Ethanol extract	Alkamides, Cichoric acid, Polysaccharides, Rutin, quercetin, and Caffeic acid	Male SD rats/ Surgically	NF-κB, COX-2, and 5-LOX	*E. purpurea* reduces damaging signals like TNF-α and IL-1β, which helps reduce joint inflammation in osteoarthritis. Additionally, it slows down the NF-κB pathway, which causes pain and swelling, and blocks the enzymes COX-2 and iNOS. All things considered, it naturally reduces joint degradation and provides OA symptom alleviation.	55-61
12	*Elaeagnus angustifolia*	Fruit, aqueous extract	Flavonoids, Phenolic compounds, Tannins, Essential fatty acids	Male albino wistar rats/MIA	NF-κB, COX-2, and MAPK	By reducing important inflammatory markers that lead to joint discomfort and damage, inclug as IL-6, TNF-α, and CRP, *E. angustifolia* helps alleviate osteoarthritis. Although it doesn't specifically target NF-κB or other pathways, it probably reduces inflammation from the top down.	62-65
13	*Peganum harmala*	Harmine	β-carboline Alkaloid,	Wistar albino rat/MIA	NF-κB	By inhibiting important inflammatory mediators such as TNF-α and IL-1β and reducing the NF-κB pathway, which causes joint destruction, harmine aids in the fight against osteoarthritis. It also reduces cartilage-degrading enzymes as such MMPs, iNOS, and COX-2. All things considered, harmine provides natural relief by shielding joints from wear and swelling.	66-68

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
14	*Astragalus mongholicus*	Fangji, huangqi, baizhu, gancao	Astragaloside IV, astragaloside II, quercetin, isoflavones, polysaccharides, amino acids, choline and betain	Male C57BL/6J mice/ Collagenase injection	NF-κB, MAPK	FJHOT helps ease osteoarthritis by reducing important inflammatory triggers that harm joints, such as IL-1β and TNF-α, that damage joints. It reduces damaging enzymes that break down cartilage, such as COX-2, iNOS, and MMPs, by blocking the TLR4/NF-κB pathway. This all-natural mixture reduces joint discomfort, preserves cartilage, and reduces swelling.	69
15	*Papaver rhoeas*	Rhoeas extract	Alkaloids, Flavonoids, Anthocyanins, Phenolic Acids	Male rats / MIA	TNF-α, COX-2, and IL-1β,	*P. rhoeas* may help with osteoarthritis by easing blood pressure and calming inflammation through its action on the Nitric Oxide (NO) pathway. It promotes improved blood flow and lessens vascular strain because it is full of natural substances like papaverine and anthocyanins. This impact, however indirect, may provide natural joint relief by reducing inflammation associated with OA.	70
16	*Pinus densiflora*	Root extract powder	Pinusols, Proanthocyanidins, Lignans, Terpenoids, Catechins	Male SD rats/ MIA	NF-κB, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2)	By reducing important inflammatory signals that lead to joint discomfort and damage, such as IL-1β and TNF-α, *P. densiflora* root extract helps relieve osteoarthritis. It inhibits the NF-κB pathway and lowers cartilage-degrading enzymes like COX-2, iNOS, and MMPs. This all-natural treatment reduces internal inflammation and promotes joint recovery.	71-81
17	*Punica granatum* L	Aqueous extracts of Eucommiae Cortex and Achyranthis Radix	Punicalagins, Ellagic acid, Anthocyanins, tannins, and Punicic acid	Male CD1 rats/ Surgically induced	NF-κB and COX-2	In particular to fight osteoarthritis, pomegranate extract reduces important inflammatory triggers that harm joints, such as TNF-α and IL-1β. It decreases the enzymes that degrade cartilage and produce pain, such as COX-2, iNOS, and MMPs, and suppresses the NF-κB pathway. In addition to protecting joints, this natural medicine promotes internal healing.	82-90

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
18	*Punica granatum* L	Pomegranate Concentrate powder	Punicalagins, Ellagic acid, Anthocyanins, Tannins, and Punicic acid	Wistar rats/MIA	NF-κB and COX-2	Through the reduction of inflammatory triggers that harm joints, such as TNF-α and IL-1β, pomegranate extract helps relieve osteoarthritis. It reduces damaging enzymes that lead to pain and cartilage degradation, such as COX-2, iNOS, and MMPs, and suppresses the NF-κB pathway. This folk cure significantly reduces swelling and promotes joint recovery.	84, 90, 91-95
19	*Sida cordifolia* L. and *Piper longum* L	Roots/aqueous extract	Ephedrine, Kaempferol, Alkaloids, Piperine, Essential oils, Flavonoids,	Rat/ Collagenase-induced OA	TNF-α, IL-6, COX-2, and NF-κB	By increasing the body's natural antioxidants, such as SOD and CAT, which combat oxidative stress that damages joints, *S. cordifolia* and *P. longum* help reduce osteoarthritis. To prevent cartilage from degrading, they also balance enzymes by increasing TIMP-1 and decreasing MMPs. When combined, they assist in maintaining joint health and naturally lower inflammation.	96-101
20	*Siraitia grosvenorii*	Residue extract/ ethanolic extract	Mogrosides, Quercetin, Saponins, Polysaccharides,	Male SD rats / MIA	TNF-α, IL-1β, IL-6, COX-2	Through the reduction of inflammatory triggers that damage joints, such as TNF-α and IL-1β, *S. grosvenorii* helps alleviate osteoarthritis. It inhibits the NF-κB pathway and lowers pain-causing and cartilage-degrading enzymes like COX-2, iNOS, and MMPs. This all-natural treatment promotes internal healing and preserves joints.	72, 102-107
21	*Styphnolobium japonicum* L	Flowers of *S. japonicum* L./ Ethanol extract	Rutin, Quercetin, Sophoraflavanone G, Isoflavonoid, Triterpenoids,	SD rats/MIA	TNF-α, IL-1β, IL-6, COX-2,	By reducing important inflammatory signals that harm joints, such as TNF-α and IL-1β, *S. japonicum* can reduce osteoarthritis. It decreases cartilage-degrading enzymes such as COX-2, iNOS, and MMPs and inhibits the NF-κB pathway. This natural ingredient significantly lowers oedema and protects joints.	108-112

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
22	*Terminalia chebula*	Fruit extract	Tannins, Chebulagic Acid, Chebulinic Acid, Ellagic Acid, Gallic Acid	Male SD rats / MIA	NF-κB, MAPK, COX-2, TNF-α, IL-1β,	*Terminalia chebula* may help ease osteoarthritis by suppressing major inflammatory signals such as IL-1β and TNF-α, which drive joint damage. It inhibits the NF-κB pathway and reduces the activity of harmful enzymes like COX-2, iNOS, and MMPs that contribute to pain, swelling, and cartilage degradation. By targeting these mechanisms, it supports cartilage protection, promotes joint repair, and helps alleviate inflammation.	79, 113-115
23	*Upanaha Choornam*	Polyherbal formulation UC	Turmeric, Ginger, Eucalyptus, Camphor, Mustard, Aloe vera, Pepper, Sandalwood	Swiss albino mice/ear oedema	NF-κB, COX-2, and LOX	*Upanaha Choornam*, a traditional Ayurvedic herbal paste, may reduce inflammation associated with osteoarthritis by reducing nitric oxide and TNF-α, two chemicals connected to joint pain. Additionally, it seems to lower COX-2 activity, which is linked to stiffness and swelling. It offers targeted treatment when applied to the afflicted area, reducing inflammation and promoting natural joint comfort.	116, 117
24	*Veronica incana*	Crude extract of *V. incana*	Flavonoids, Tannins, Phenolic compounds, Essential Oils	Male SD rats/ MIA	COX-2, LOX, TNF-α, IL-1β	By reducing inflammation triggers like IL-1β and TNF-α that cause joint discomfort and damage, *V. incana* helps relieve osteoarthritis. It inhibits the NF-κB pathway and lowers cartilage-degrading enzymes like COX-2, iNOS, and MMPs. This all-natural herb significantly reduces oedema and promotes joint recovery.	118-122
25	*Tribulus terrestris*	Dried fruits/ ethanolic extract	Saponins, flavonoids, alkaloids, tannins, steroidal	Female, LEW/ SSNHSD rats/ MIA	TNF-α, IL-1β, and nuclear factor kappa B (NF-κB)	By lowering important inflammatory indicators that cause joint pain and swelling, such as IL-6 and TNF-α, *T. terrestris* helps treat osteoarthritis. To preserve cartilage, it increases natural antioxidants like SOD and CAT while decreasing enzymes like COX-2 and iNOS. This herbal medicine promotes healthy joint movement and subtly reduces inflammation.	123-127

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
26	*Cissus quadrangularis, Withania somnifera*	Combine the herbal extract	Ketosterones, triterpenoids, withanolides, alkaloids, ketosterones, flavonoids, saponins, steroidal lactones,	Swiss albino rats/Type II collagen	NF-κB Pathway, MMP	Together, *C. quadrangularis* and *W. somnifera* reduce osteoarthritis by inhibiting important inflammatory mediators such as IL-6 and TNF-α. They increase the body's natural antioxidants, such as SOD and GSH, while decreasing pain-causing enzymes, such as COX-2 and iNOS. This herbal combination promotes smooth mobility, lowers swelling, and protects joints.	33, 128-132
27	*Rosa canina* L. and *Camellia sinensis*	Dried rosehip fruit /aqueous extract	Epigallocatechin Gallate (EGCG), epicatechin, epicatechin gallate, galactolipids, quercetin, kaempferol, triterpenoids, essential fatty acids	Male Wistar rats/MIA	COX-2, NF-κB	RHP and GTSE combined showed enhanced anti-inflammatory and chondroprotective effects, offering a promising therapy for osteoarthritis.	133-138
28	*Uncaria gambir* and *Morus alba*	Leaves, root/ ethanolic extract	Cat's claw tannins, gambir tannins, rhynchophylline, isorhynchophylline, flavonoids, resveratrol, anthocyanins, syringic acid	Male SD rats/ MIA	TNF-α, IL-1β, IL-6, and NF-κB	This study demonstrates how UP3005, a combination of Morus alba and *Uncaria gambir*, successfully lowers osteoarthritis-related joint inflammation and cartilage destruction. By focusing on important inflammatory pathways like NF-κB and cytokines like TNF-α and IL-1β, it helps preserve bone structure and cartilage. According to these results, UP3005 might provide a disease-modifying, natural alternative for treating OA.	139-155
29	*Agerantum conzoides*	Leaves/ethanol	Quercetin, luteolin, kaempferol, Ageratochromene, saponins, eucalyptol, thymol	White male SD rats, MIA	NF-κB, MMP	This study demonstrates that by repairing cartilage indicators and reducing TNF-α levels, *Ageratum conyzoides* extract helps reduce joint inflammation in osteoarthritis. Similar to quercetin, these substances function by inhibiting important inflammatory signals, including COX-2 and NF-κB. These findings imply that it might promote joint health by reducing inflammation and protecting cartilage.	156-158

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
30	*Boswellia serrata*	*B. serrata* gum resin extracts	Quercetin, luteolin, kaempferol, ageratochromene, saponins, eucalyptol, thymol,	Female SD rats/MIA	NF-κB, MMP	According to this study, *Boswellia serrata* resin reduces important markers, including TNF-α and IL-1β, which helps reduce joint inflammation in osteoarthritis. Its natural boswellic acids reduce inflammation caused by NF-κB and block enzymes like 5-LOX. As a result, it naturally slows the progression of OA and protects cartilage.	160-166
31	*Caragana sinica*	Root, aqueous extract	Quercetin, kaempferol, triterpenoids, phenolic compounds, polysaccharides, formononetin, saponins	Rat/MIA	MAPKs, NF-κB	This study demonstrates that by inhibiting important signals like NF-κB, *caragana sinica* extract helps lower joint inflammation in osteoarthritis. It reduces cartilage-damaging enzymes and cytokines such as iNOS, COX-2, and MMPs. The extract helps to naturally reduce OA symptoms and protect joints by reducing this inflammatory reaction.	167-170
32	*Carya illinoinensis* and *Pistacia vera*	Dietary supplementation	Tannins, ellagic acid, catechins, epicatechins, tocopherols, omega-3 fatty acids, resveratrol, gallic acid, quercetin, kaempferol, triterpenoids, β-sitosterol	Male albino rats/complete Freund's adjuvant	NF-κB pathway, MMP, COX, and LOX pathways	This study shows that pecan and pistachio extracts help ease joint inflammation in osteoarthritis by lowering harmful markers like TNF-α and IL-1β. Their high polyphenol and antioxidant content probably soothes the NF-κB pathway and inhibits important enzymes like COX-2 and iNOS. When combined, they help preserve cartilage and lessen the natural damage caused by OA.	171-174
33	*Centella asiatica*	Leaves/ ethanolic extract	Asiaticoside, madecassoside, asiatic acid, madecassic acid, quercetin, kaempferol, triterpenoids	Male SD rats/ MIA	NF-κB Pathway, MMP	According to this study, *Centella asiatica* extract reduces TNF-α and increases cartilage health indicators like COMP to help reduce joint inflammation in osteoarthritis. Triterpenoids and flavonoids, two of its natural constituents, function by inhibiting the NF-κB pathway and lowering toxic enzymes like iNOS and COX-2. As a result, it naturally reduces OA symptoms and promotes joint protection.	175-178

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
34	*Zingiber officinale Roscoe*	Aqueous ginger extract	Gingerol, shogaol, zingerone, curcumin, beta-caryophyllene	Mice with collagen-induced arthritis	COX-2, LOX	By reducing important indicators, including TNF-α, IL-1β, and oxidative stress, ginger extract reduces joint inflammation in osteoarthritis, according to this study. The NF-κB pathway is calmed, and dangerous enzymes like COX-2 and iNOS are blocked by its natural chemicals, gingerols and shogaols. Ginger, therefore, promotes joint health and naturally lessens cartilage degeneration.	179-183
35	*Colocasia esculenta* root tuber and *Zingiber officinale* rhizome	Aqueous extracts	Catechins, epicatechins, quercetin, kaempferol, polysacchaWistar 6-shogaol, 6-gingerol, 8-gingerol, and 10-gingerol. zingerone, zingiberene, β-sesquiphellandrene	Male Wistar rats/MIA	NF-κB pathway, COX and LOX pathways, MAPK pathway, Wnt/β-catenin signalling pathway, and TGF-β/ SMAD pathway	This study shows that *Colocasia esculenta* and *Zingiber officinale* help calm joint inflammation in osteoarthritis by lowering TNF-α and boosting cartilage health. Together, their flavonoids and natural antioxidants inhibit NF-κB signalling and lower dangerous enzymes like iNOS and COX-2. This mixture promotes natural long-term joint protection and reduces joint deterioration.	184, 185
36	*Glycyrrhiza glabra*	Glycyrrhizin	Glycyrrhizin, liquiritin, liquricidin, saponins, glabridin	SD rats/MIA	NF-κB, COX-2, 5-LOX,	This study demonstrates that by reducing TNF-α and preserving cartilage, licorice extract can minimise joint inflammation in osteoarthritis. Its natural substances, such as glycyrrhizin, function by inhibiting dangerous enzymes like COX-2 and iNOS and reducing the NF-κB pathway. Consequently, it promotes better cartilage naturally and reduces joint injury.	186-191
37	*Glycine soja*	Leaf and stem extract	Genistein, daidzein, glycitein, saponins, phospholipids, proteins and peptides, linoleic acid, oleic acid	Male SD rats/ MIA	Pathways like IL-1β, IL-6, TNF-α, COX-2, MMPs	This study demonstrates that by reducing TNF-α and IL-1β levels, extracts from the leaves and stems of *Glycine soja* help reduce joint inflammation in osteoarthritis. The NF-κB pathway is calm and dangerous enzymes like COX-2 and iNOS are blocked by its natural flavonoids and isoflavones. This naturally reduces OA symptoms and preserves cartilage.	192, 193

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
38	*Grape seed*	Grape seed oil/ avocado fruits	Proanthocyanidin, quercetin, kaempferol, gallic acid, caffeic acid, linoleic acid, and tannins	Male SD rats/ Surgical method	COX-2, NF-κB	This study demonstrates that by repairing cartilage and enhancing joint structure, *grape seed* oil reduces joint inflammation in osteoarthritis. Its natural polyphenols, including catechins and proanthocyanidins, are thought to lower dangerous enzymes like COX-2 and iNOS and soothe the NF-κB pathway. The tissue healing indicates its potent anti-inflammatory properties even in the absence of direct cytokine data.	194-198
39	*Psidium guajava*	Hydro-ethanolic extract/guava fruit and leaf	Quercetin, kaempferol, catechins, gallic acid, ellagic acid, tannin, vitamin C, essential fatty acids, beta-carotene, lycopene,	SD rats/Papain solution	COX-2, TNF-α, IL-1β, and IL-6.	This study shows that guava leaf extract helps reduce joint inflammation in osteoarthritis by lowering TNF-α levels and supporting cartilage health. Its natural components, like flavonoids and tannins, function by inhibiting dangerous enzymes like COX-2 and iNOS and reducing the NF-κB pathway. As a result, it naturally slows the progression of OA while protecting joints.	199-203
40	*Rosmarinus officinalis* L. and *Mentha piperita*	Rosemary and peppermint essential oils	Rosmarinic acid, carnosic acid, carnosol, 1,8-cineole, menthol, menthone, rosmarinic acid, flavonoids	Male and female Wistar rats/MIA	COX-2, NF-κB,	This study demonstrates that by reducing TNF-α, IL-1β, and oxidative stress, peppermint and rosemary oil nanoemulsions help reduce joint inflammation in osteoarthritis. Their natural compounds, like menthol and 1,8-cineole, block the NF-κB pathway and reduce harmful enzymes like COX-2 and iNOS. A natural way to OA relief is provided by the healthier cartilage and reduced joint degeneration that occurs.	204-208
41	*Rosmarinus officinalis* and *Populus alba*	Leaves and flowers/ essential oils	Rosmarinic acid, carnosic acid, carnosol, 1,8-cineole, salicylates, quercetin, phenolic acids, tannins	Wistar rats/MIA	COX-2, NF-κB,	Essential oils extracted from Rosmarinus officinalis and Pterocarpus alba significantly reduced Mankin scores, demonstrating protective effects against osteoarthritis.	209

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
42	*Schisandra chinensis*	Leaves/ ethanolic extract	Triterpenoids, lignans, flavonoids, polysaccharides, phenolic compounds, essential oils	Male SD rat/ MIA	NF-κB, MMP	According to this study, *Schisandra chinensis* reduces TNF-α and increases natural antioxidants like SOD to help reduce joint inflammation in osteoarthritis. Its potent lignans and polyphenols lower dangerous enzymes like COX-2 and iNOS and soothe the NF-κB pathway. Consequently, it preserves cartilage and promotes joints that are healthier and less inflammatory.	210, 211
43	*Scoparia dulcis*	Crude extract	Scoparone, Quercetin, Luteolin, Coumarins, Triterpenoids, Saponins,	Wistar rats/MIA	COX-2, NF-κB,	This study demonstrates that by reducing oxidative stress markers like MDA and TNF-α, *Scoparia dulcis* extract can reduce joint inflammation in osteoarthritis. Its natural flavonoids and polyphenols reduce dangerous enzymes like COX-2 and iNOS and block the NF-κB pathway. In a mild, organic manner, this helps preserve cartilage and reduce joint degeneration brought on by OA.	212-216
44	*Ziziphus jujuba*	Hydroalcoholic extract of *Ziziphus jujuba* fruits	Saponins, Flavonoids, Alkaloids, Phenolic Acids, Triterpenes	NMRI mice/MIA	Interleukin-1β (IL-1β), TNF-α, and cyclooxygenase-2 (COX-2).	This study shows that *Ziziphus jujuba* extract helps reduce joint inflammation in osteoarthritis by lowering TNF-α and boosting antioxidant defences like SOD. Its natural flavonoids and saponins inhibit enzymes like COX-2 and iNOS and help the NF-κB pathway. It thereby preserves cartilage and aids in the natural alleviation of OA symptoms.	217-219
45	*Eucommia ulmoides* Olivz	Bark aqueous extract	Geniposide, Eucommiol, Lignans, Chlorogenic Acid, Flavonoids,	SD rats/MIA	NF-κB, COX-2, and MAPK	According to this study, the leaf extract of *E. ulmoides* reduces oxidative stress and TNF-α while increasing the body's natural antioxidants, such as SOD, to help reduce joint inflammation in osteoarthritis. Flavonoids and iridoids, two of its potent plant chemicals, can inhibit dangerous enzymes like COX-2 and iNOS and soothe the NF-κB pathway. This all-natural method slows the progression of OA and protects cartilage.	224-227

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
46	*Lawsonia inermis* and *Ricinus communis*	Dry leaves of *Lawsonia inermis* L./ Aqueous extract	Lawsone, Flavonoids, Tannins, Saponins, Ricinoleic acid, Triterpenoids, Phenolic Compounds, Saponins	Male Wistar rats/MIA	Nuclear factor-kappa B (NF-κB)	This study demonstrates that by reducing oxidative stress and TNF-α, combining leaf extracts from *L. inermis* with R. communis helps reduce joint inflammation in osteoarthritis. Their natural substances, like terpenoids and flavonoids, inhibit enzymes like iNOS and COX-2 and soothe the NF-κB pathway. They work together to preserve cartilage and lessen joint degeneration brought on by OA.	228-232
47	*Andrograph paniculata*	Leaf/ ethanol extract	Andrographolide, 14-deoxyandrographolide, and neoandrographolide	Male SD rats/ MIA	IL-1β, IL-6, TNF-α, iNOS and COX-2	By reducing important inflammatory signals in the joints, the therapy helps reduce osteoarthritis. It inhibits the NF-κB pathway, which causes tissue damage and swelling, and reduces dangerous cytokines, including TNF-α and IL-1β. This promotes healthier joint function, preserves cartilage, and lessens pain and inflammation.	233-237
48	*Alpinia oxyphylla*	Dried fruit/ ethanol extract	Nootkatone, chrysin, tectochrysin, izalpinin, kaempferide, steroids and their glycosides	Male SD rats/ MIA	IL-1β, IL-6, TNF-α	The compound helps protect joints in osteoarthritis by calming inflammation at its source. It inhibits the NF-κB pathway, which causes tissue damage and swelling, and reduces important cytokines, including TNF-α and IL-1β. This helps maintain cartilage and joint function in addition to reducing pain and stiffness.	238-242
49	*Cynanchum wilfordii*	Root/aqueous extract	Cynandione A, auriculosides I-IV, cynanauriculosides I and II, haneoekinols, quercetin, tamarixetin and other constituents including cinnamic acid, sinapic acid.	Male SD rats/ Carrageenan Injection	COX-2, MMP-13, NF-κB	The treatment reduces osteoarthritis by inhibiting the NF-κB pathway, which causes inflammation in the joints. It reduces damaging enzymes and cytokines that lead to cartilage degradation, discomfort, and oedema. This focused action promotes improved mobility and comfort while safeguarding joint structure.	243-247

Table 1. Continued...

S. No.	Scientific name	Part/ extract	Active constituents	Animal/Model	Pathway	Result	References
50	*Litsea japonica*	Fruit/ethanol extract	Hamabiwalactone A and B	Male SD rats/ MIA	IL-6, IL-1β, and TNF-α	By inhibiting the NF-κB pathway and lowering important inflammatory signals like TNF-α and IL-1β, the therapy reduces osteoarthritis. Additionally, it reduces COX-2 and iNOS, two enzymes that cause pain and oedema. When combined, these activities enhance joint comfort and mobility while preserving cartilage.	[248-251]

4.2 *Angelica gigas* Nakai (*Apiaceae*)

Korean angelica is widely recognised for its anti-inflammatory and antioxidant properties. To understand how it protects against OA caused by monosodium iodoacetate (MIA), an experiment was carried out over 4 weeks using 7-week-old male Sprague–Dawley rats. Rats received 200 mg/kg of Korean angelica every day for 14 days, starting 7 days after an MIA injection (50 µl with 80 mg/ml) was injected into their joints. The study demonstrated that Korean *angelica* decreases inflammation by inhibiting several critical factors, specifically those mediated by the NF-κB signalling pathway, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, IL-6, and IL-1β. Additionally, it lowers the levels of matrix metalloproteinases (enzymes that break down joint tissue). It increases tissue inhibitors of these molecules' enzymes, improving the reduction of the breakdown of the joints' extracellular matrix[29-31].

4.3 *Euphausia superba* (*Euphausiidae*)

Antarctic oil has shown effectiveness in reducing arthritis symptoms, particularly in osteoarthritis induced by MIA. In MIA-treated animals, inflammatory marker levels, including levels of serum PGE2, IL-1, IL-6, and TNF, were increased but subsequently decreased post-FJH-KO supplementation. The treatment of FJH-KO given at 100 mg/kg body weight and 150 mg/kg body weight suppressed the mRNA expression of catabolic factors while boosting the expression of anabolic factors that promote joint health. Furthermore, it decreased the mRNA levels of inflammatory mediators, enhancing its protective effects. The findings suggest that FJH-KO aids in restoring the smooth surface of articular cartilage and improving the inflammatory response linked to osteoarthritis. Its anti-osteoarthritic effects are primarily linked to the protection of cartilage, as it reduces inflammation and prevents tissue degradation by downregulating pro-inflammatory cytokines. According to these results, FJH-KO may be a useful medication for balancing or managing osteoarthritis[31-34].

4.4 *Aucklandia lappa* (*Asteraceae*)

Kuth (*A. lappa* root) is known for its bioactive compounds and traditional use in treating bone diseases and other health conditions. This study evaluated its therapeutic effects on OA. In an acetic acid-induced pain model in mice, *A. lappa* notably alleviated pain, showing anti-nociceptive properties. In rats, OA was induced using MIA, and *A. lappa* demonstrated significant anti-inflammatory effects. The bioactive compounds- costunolide, dehydrocostus lactone, dihydrocostunolide, costus lactone, α-costol, and Saussurea lactone—are essential to its therapeutic effects. In particular, costunolide modifies inflammatory pathways, including NF-κB and heat shock protein signalling in LPS-activated macrophages, leading to a reduction in mediators such as TNF-α, COX-2, IL-1β, iNOS, and IL-6. Overall, *A. lappa* root extract effectively reduced inflammation and pain in MIA-induced OA, acetic acid pain models, and LPS-activated macrophages, highlighting its potential as a natural therapeutic for osteoarthritis management[35-38].

4.5 *Balsamodendron mukul* (*Burseraceae*)

Guggul (BDM gum resin) contains active compounds like polyphenols and guggul-sterone, which exhibit anti-osteoarthritic properties. In this study, the induction of OA in rats was performed through the intra-articular injection of papain and cysteine. The degradation of collagen in OA is primarily mediated by matrix metalloproteinases (MMP-1, MMP-8, and MMP-13) and Reactive Oxygen Species (ROS), leading to the degradation of cartilage. Treatment with BDM gum resin extract significantly increased total protein and collagen content in the articular cartilage compared to the OA group. Histological analysis showed thicker cartilage and improved trabecular density in the subchondral bone. Oral administration of BDM extract reduced OA-related pain, regenerated the cartilage matrix, and enhanced bone components. These findings suggest that BDM gum resin extract may be a promising natural therapy for reversing cartilage damage and reducing OA-related inflammatory pain[37-39].

4.6 *Boswellia serrate* (*Burseraceae*)

Boswellia serrate, referred to as Salai, boasts active components that display anti-inflammatory effects, including Acetyl-11-Keto-β-Boswellic Acid (AKBA), β-Boswellic Acid, and 11-Keto-β-Boswellic Acid (KBA). These factors are strong anti-inflammatory agents that are selective non-redox inhibitors of 5-Lipoxygenase (5-LOX), which is critical in the management of inflammatory diseases. An assessment of the efficacy of LI13019F1 (Serratrin®) in the management of OA was conducted in an MIA-induced OA model in Sprague-Dawley rats over a period of 28 days. The rats demonstrated statistically significant improvement in their body-weight-bearing capacity, suggesting pain relief and improved joint function, with doses of 150 mg/kg and 300 mg/kg of LI13019F1. Additionally, LI13019F1 showed promising protective effects on the cartilage and maintained chondrocyte physiology, displaying a mechanism to be utilised for OA management. Primary phytoconstituents of *Boswellia serrata* are quercetin, luteolin, kaempferol, ageratochromene, saponins, eucalyptol, and thymol that interact in known inflammatory pathways, such as NF-κB and Matrix Metalloproteinases (MMPs), influencing cartilage catabolism and inflammatory processes within osteoarthritis. Overall, the data indicate *B. serrata* gum and its active products, specifically LI13019F1, possess anti-inflammatory and chondroprotective properties, potentially becoming a therapeutic agent for osteoarthritis[40,41].

4.7 *Crataegus sinica* (*Rosaceae*)

Crataegus sinica (Rosaceae), commonly known as hawthorn, contains bioactive constituents such as quercetin, rutin, vitexin, hyperoside, chlorogenic acid, caffeic acid, oligomeric proanthocyanidins, ursolic acid, oleanolic acid, and essential oils, which exhibit anti-osteoarthritic properties. The therapeutic effects of *Crataegus sinica* Extract (CSE) are linked to the anti-inflammatory efficacy of CSE on the suppression of the NF-κB pathway, MMPs, COX, and LOX pathways, evaluated at 100, 200, and 300 mg/kg (for four weeks, daily, orally) and compared with ibuprofen (40 mg/kg). An acute toxicity study in male albino rats indicated no toxicity or fatality seen at doses of 3000 mg/kg for two weeks. CSE resulted in a decreased degree of joint inflammation and pathological damage, along with lowered serum levels of TNF-α, IL-6, Hyaluronic Acid (HA), and CTX-II, while alleviating MIA-induced pain behaviours in a rat osteoarthritis model. These findings suggest CSE has chondroprotective and pain-relieving effects, making it a promising natural therapy for osteoarthritis[42,43].

4.8 *Curcuma longa* L. (*Zingiberaceae*)

Curcumin, a key bioactive compound derived from turmeric (*Curcuma longa*), has garnered attention for its significant anti-osteoarthritic properties. The primary active constituents, including demethoxycurcumin, bisdemethoxycurcumin, turmerone, and ferulic acid, exhibit Anti-inflammatory and cartilage-protective effects through the modification of key molecular pathways, such as NF-κB, MMPs, COX-2, and LOX. Post-traumatic OA model: An osteoarthritis model was created in adult The medial meniscus was destabilised (DMM) in C57BL/6 mice. Mice were treated with curcumin via oral gavage (50 mg/kg) or topically via curcumin nanoparticles for eight weeks. Both treatments significantly reduced OA progression, alleviated knee pain, and preserved cartilage structure. Mechanistically, curcumin regulated key proteinases, including MMP-13 and ADAMTS5, in chondrocytes and inhibited pro-inflammatory adipokines and

mediators in the infrapatellar fat pad, which are important for cartilage homeostasis. These studies highlight the therapeutic potential of curcumin as a natural treatment for OA, providing a multi-targeted approach to inflammation, cartilage degeneration, and pain relief. Additional clinical trials will be needed to validate its true efficacy and better utilise it as a therapeutic approach[44-48].

4.9 *Dipsacus asteroids* (*Caprifoliaceae*)

Dipsacus asteroids (*Caprifoliaceae*) and *Patersonia umbrosa* (*Iridaceae*), (*D. asteroids*) and yellow flags (*Polygonatum umbrosum*) are emerging as promising anti-osteoarthritic agents due to their bioactive phytoconstituents, including saponins, quercetin, kaempferol, aucubin, and phenolic compounds. These active components inhibit key inflammatory pathways like NF-κB, COX-2, and 5-LOX, which play a role in osteoarthritis progression. The results of D. asperoides (the previous paragraph refers to *D. asperoides* were used in the possible effects of DAE (*Dioscorea alata* Extract) and PUE (*Pterocarpus umbrosa* extract), which were evaluated in rats with knee OA induced by MIA (monosodium iodoacetate). The rats were treated for 21 days with daily doses of 200 mg/kg DAE and PUE. Both DAE and PUE improved weight-bearing distribution on the hind limbs, decreased serum production of cytokines, and improved histopathological changes in the knee OA-affected tissues. PUE was more effective than DAE for balancing, decreasing pain in the joint, and improving mobility. Overall, *P. umbrosa* may be a more efficacious and better alternative option for treating OA than *D. asperoides*, providing a natural approach for people to treat joint pain and inflammation from OA. More studies are needed to better understand the clinical application and optimisation of DAE and PUE for OA[49-52].

4.10 *Dashmoolarishta* (Formulation)

Dashmoolarishta (Formulation), the root of *Dipsacus asperoides*, traditionally, a plant *D. asperoides*, known for its analgesic and anti-inflammatory attributes, *D. asperoides* is used to treat OA, a condition characterised by degenerative cartilage degeneration. To assess its effect, a rat model of OA induced by MIA was administered an ethanolic extract of *D. asperoides* at a dose of 200 mg/kg of body weight daily for 21 days. Results showed that the rats treated with *D. asperoides* significantly reduced several symptoms of OA, such as joint swelling; it maintained the anatomical and histological status of the knee while reducing its diameter, providing a protective effect against the disease. *D. asperoides* demonstrates, in comparison to traditional treatment, a reduction in the possible degeneration of cartilage and improved overall joint well-being. For a deeper understanding of the molecular mechanisms involved, a gene expression profile was assessed on articular cartilage tissue from OA rats. Next-generation RNA sequencing demonstrated that treatment of rats with *D. asperoides* modulated numerous processes, specifically the WNT/β-catenin signalling pathway essential to cartilaginous repair homeostasis, while demonstrating that *D. asperoides* may regulate cellular features responsible for maintaining the integrity of the joint in OA. In summary, the study demonstrates that *D. asperoides* extract exerts a protective effect against OA in rats by reducing inflammation, preserving joint structure, and modulating critical signalling pathways involved in cartilage health. Although more research is needed to confirm its clinical efficacy and applicability in human populations, these findings suggest that DAE may be a promising natural medication for treating osteoarthritis[50,53,54].

4.11 *Echinacea purpurea* (*Asteraceae*)

Echinacea purpurea (*Asteraceae*), commonly known as purple coneflower, has been investigated for possible OA treatment benefits. In a recent experiment, Regular physical activity offers a variety of advantages for the body, such as reducing cardiovascular risk factors and cardiovascular diseases. A study demonstrated an association between physical activity and a lower cardiovascular mortality rate and risk of cardiovascular diseases. Exercise helps to control or modify the established risk factors of heart disease, such as hypertension and hyperlipidemia. Moreover, there are either biochemical or physiological changes caused by aerobic or strength training exercise to improve vascular and metabolic health as a form of disease prevention. The active constituents of *Echinacea purpurea*, including alkamides, cichoric acid, polysaccharides, rutin, quercetin, and caffeic acid, are believed to contribute to the anti-inflammatory and cartilage-protective effects. These findings suggest that *E. purpurea* extracts,

especially in the nano-formulation, have significant potential in modulating key biomarkers associated with OA, promoting cartilage preservation, and offering a natural therapeutic approach for osteoarthritis management[55-61].

4.12 *Elaeagnus angustifolia* (*Elaeagnaceae*)

Elaeagnus angustifolia (*Elaeagnaceae*), commonly known as Russian Olive, has possible therapeutic benefits for OA that have been studied. In research comprised of twenty-eight adult male albino Wistar rats aged 12-14 weeks with weights varying from two hundred to two hundred and fifty grams (200-250 g), osteoarthritis was induced *via* an intra-articular injection of monosodium iodoacetate. Monosodium iodoacetate is known to cause osteoarthritis by inhibiting glycolytic pathways in the joint tissue, resulting in chondrocyte death and increased inflammatory responses. The results demonstrated that the injection of monosodium iodoacetate resulted in a significant reduction of the cycle number of joint oscillations, indicating a joint dysfunction. Significantly, the treatment group receiving the *E. angustifolia* extract had a significantly improved cycle number and maximum peak of joint oscillations compared to the monosodium iodoacetate group, demonstrating that joint dysfunction had improved joint function. Moreover, the administration of *E. angustifolia* extracts increased Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) activities of antioxidant enzymes, where SOD (P=0.011) and GPx (P=0.05) were significantly improved compared to the MIA group. Furthermore, *E. angustifolia* extracts significantly decreased levels of malondialdehyde (MDA) (P=0.000) in comparison to the MIA, corresponding to a reduction of a biomarker of oxidative stress. The results suggest that *E. angustifolia* extract improves antioxidant enzyme activity and reduces oxidative stress, reducing joint friction, all combined, where we can conclude *E. angustifolia* extract is a promising natural therapeutic agent for osteoarthritis intervention[62-65].

4.13 *Peganum harmala* (*Zygophyllaceae*) Harmine

Peganum harmala (*Zygophyllaceae*) Harmine, a bioactive compound derived from *Peganum harmala* (Wild Rue), has shown promising effects in attenuating OA through its antioxidant and anti-inflammatory properties. *In vitro* studies were conducted using LPS-induced RAW264.7 cells, where harmine was administered at concentrations of 5 and 10 mM. *In vivo*, in rats, OA was initiated through an intra-articular injection of monosodium iodoacetate (MIA, 2.5 mg in 10 mL of saline). One week before and 25 days after the MIA injection, the rats received harmine treatment at doses of 25 and 50 mg/kg. The results also demonstrated that harmine treatment significantly reduced OA-related oxidative stress and inflammation. Furthermore, in both MIA-induced rats and LPS-exposed RAW264.7 cells, it successfully reduced pro-inflammatory indicators such as PGE-2, NO, and other inflammatory mediators. Additionally, administering harmine reduced oxidative damage indicators like MDA and boosted antioxidant enzyme activities such as Glutathione (GSH), Catalase (CAT), and SOD. Proving its strong antioxidant properties. In the OA model, harmine reduced tissue damage and bone loss, according to histological examination. These findings suggest that harmine may help cure osteoarthritis by reducing oxidative stress and inflammation. To fully understand its precise therapeutic mechanisms in the treatment of OA, more research is necessary[66-68].

4.14 *Astragalus mongholicus* (*Fabaceae*)

Astragalus mongholicus (*Fabaceae*), also referred to as Mongolian milkvetch, such as astragaloside iv, astragaloside ii, quercetin, isoflavones, polysaccharides, amino acids, choline, and betaine, has shown great promise in the treatment of OA. These bioactive ingredients primarily work as medicines by blocking important inflammatory pathways, such as NF-κB and MAPK, which contribute to the development of OA. The effectiveness of *A. mongholicus* as a treatment for osteoarthritis (KOA) of the knee was investigated in recent studies. In particular, a decoction of *Astragalus mongholicus* (FJHQT) increased synovial lymphatic vessel formation in KOA joints, revealing improved lymphatic drainage function. The aforementioned lymphatic improvement helps support articular cartilage architecture and postpone joint degeneration, especially early in the KOA process. According to the findings, *Astragalus mongholicus* may be efficacious in preventing and providing early treatment for KOA through enhanced joint health and decelerating the

degenerative processes of KOA. Future studies will be needed to fully understand how these compounds function as pharmaceutical methods for treating OA[69].

4.15 *Papaver rhoeas* (*Papaveraceae*)

Papaver rhoeas (*Papaveraceae*), popularly referred to as Corn Poppy or Flanders Poppy, has been examined for potential medicinal effects on OA and its relationship with the nitrergic system. In a recent study, OA was induced in 35 male rats via MIA injections into their knee joint. After that, the rats received a 30-day treatment with an aqueous extract of *P. rhoeas*. After 30 days, blood pressure and its impact on the nervous system were examined. In OA rats, *P. rhoeas* aqueous extract dramatically lowered blood pressure. Additional testing with the Nitric Oxide Synthase (NOS) inhibitor L-NAME indicates that the nitrergic system may be involved in its blood pressure-lowering action. Compared to the control group that received L-NAME alone, the co-administration of the *P. rhoeas* extract and L-NAME resulted in a decrease in systolic and mean arterial pressure as well as an increase in heart rate. Through its modulation of the NO pathway, which is crucial for blood pressure regulation and sympathetic nervous system activity, the extract may help counteract the hypertensive effects caused by L-NAME. According to these results, *P. rhoeas* may have anti-nitrergic effects and be useful as a treatment for OA patients' blood pressure. However, more research is needed to determine the precise processes underlying this impact, including whether it functions through central mechanisms or at the level of cardiovascular receptors. To elucidate these mechanisms and validate the possible clinical uses of *P. rhoeas* in OA and associated cardiovascular disorders, more research is required[70].

4.16 *Pinus densiflora* (*Pinaceae*)

Pinus densiflora (*Pinaceae*) Japanese Red Pine Extract (PDREP) has shown notable anti-inflammatory and joint protective advantages in both *in vitro* and *in vivo* OA. A MIA injection caused OA in Sprague-Dawley (SD) rats, which were then given PDREP at 100, 300, and 500 mg/kg or MSM at 300 mg/kg as a positive control every day for six (6) weeks. The results showed that PDREP markedly reduced the expression levels of mediators, cytokines, and MMPs linked to inflammation in both the rat models of osteoarthritis caused by MIA and the IL-1β-induced SW1353 chondrosarcoma cells. PDREP also decreased the phosphorylation levels of MAPKs and NF-κB proteins, which are master regulators in the inflammatory response. Additionally, treatment with PDREP in the rat models decreased clinical signs of OA. In addition, histological joint damage was reduced. This data supports the role of PDREP in inhibiting the activities of MMPs and inflammatory mediators, likely through the modulation of the MAPKs/NF-κB signalling pathways to mediate its therapeutic product. PDREP shows great possibility as a treatment or functional product for OA, reducing inflammation and slowing the progression of cartilage degeneration. However, further studies are necessary to evaluate the clinical efficacy and understand the mechanisms of action[71-81].

4.17 *Punica granatum* L. (*Lythraceae*) Pomegranate

Punica granatum L. (*Lythraceae*) Pomegranate, known for its active phytoconstituent compounds like punicalagins, ellagic acid, anthocyanins, tannins, and punicic acid, has shown promising therapeutic effects in the management of OA. The main actions are through inhibiting inflammatory pathways, particularly the pathways involving NF-κB and COX-2. In the surgically induced OA rat model, the anterior cruciate ligament was transacted, followed by a partial medial meniscectomy to simulate the pathogenesis of OA. The medial joint capsule was incised during this surgical technique, and the capsule and skin were then closed by suturing with dissolvable materials. The study emphasised the synergistic effects of pomegranate with a combination of herbal extracts, such as *Arthrospira* (AR) and *Echinacea purpurea* (EC). When these extracts were combined in different ratios (2:1, 4:1, and 1:1), the anti-OA effects were noticeably stronger than when each ingredient was used alone. These results imply that pomegranates, when combined with *Arthrospira* and *Echinacea*, have anti-inflammatory properties and encourage chondrogenic activity, offering a potential natural treatment option for OA[82-90]. Another study related to mixed formulation of pomegranate Concentrate Powder: *Eucommiae Cortex: Achyranthis Radix* for OA. The disease was induced through a joint injection of 3 mg of MIA into the joint

space of the left leg. The study then assessed several key active pomegranate compounds, including punicalagin, ellagic acid, anthocyanins, tannins, and punicic acid, for their ability to alleviate OA symptoms. These compounds may interact with inflammatory pathways associated with OA progression. The study found that PEA-Mix, a combination of the compounds (delivered at 50 mg/kg), significantly alleviated OA symptoms (cartilage receives damage, inflammation, synovial membrane fibrosis, knee stiffness, and pain). The effect of PEA-Mix on OA symptoms was comparable to that of diclofenac sodium (used at a dose administered at 2 mg/kg, a widely used anti-inflammatory agent. Importantly, PEA-Mix supported the growth of cartilage cells and increased the production of ECM (extracellular matrix), an important molecule for healthy cartilage development (unlike diclofenac). In conclusion, PEA-Mix may reduce inflammation and protect cartilage, while also facilitating cartilage repair and regeneration. Collectively, the findings presented here support further assessment of the potential efficacy of PEA-Mix as a pomegranate-based natural treatment for OA, via preclinical and clinical studies[84,90,91-95].

4.18 *Sida cordifolia* L. (*Malvaceae*) and *Piper longum* L. (*Piperaceae*)

Sida cordifolia L. (*Malvaceae*) and *Piper longum* L. (*Piperaceae*) Flannel weed (*Sida cordifolia*) and long pepper (*Piper longum*) were studied for their antioxidant properties and phenolic content, along with their ability to counteract OA in a rat model. Collagenase II was injected into the knee joint to cause OA. The effects of these plants were evaluated, including molecular analysis of the synovium and the soft tissue lining the joint. The results showed that both plants reduced the overexpression of Matrix Metalloproteinases (MMPs), enzymes responsible for cartilage breakdown, and restored the levels of Tissue Inhibitors of Metalloproteinases (TIMPs), which protect cartilage. This indicates that *S. cordifolia* and *P. longum* can help prevent cartilage degradation in OA. Main active compounds in these plants include ephedrine, quercetin, kaempferol, alkaloids, piperine, essential oils, and flavonoids. These substances target TNF-α, IL-6, COX-2, and NF-κB through anti-inflammatory mechanisms. These results imply that by lowering inflammation and preserving cartilage, these herbs may be used as natural treatments to treat OA[96-101].

4.19 *Siraitia grosvenorii* (*Cucurbitaceae*)

The Cucurbitaceae species *Siraitia grosvenorii,* the "single fruit," or monk fruit, may be used to treat OA because it contains active compounds such as microsites, quercetin, saponins, and polysaccharides that interact with inflammatory pathways like TNF-α, IL-1β, IL-6, and COX-2. A study conducted on male Sprague Dawley rats examined the efficacy of monk fruit extract (SGRE). The study showed that SGRE diminished inflammation by blocking the MAPK and NF-κB signalling pathways. SGRE reduces cytokine (IL-1β, IL-6, and TNF-α) and inflammatory mediator (iNOS, COX-2, 5-LOX, PGE2, and LTB4) levels. Further, SGRE promotes cartilage protection by lowering extracellular matrix-degrading enzymes (MMPs) and promoting cartilage synthesis through genes such as SOX9, ACAN, and COL2A1. These results indicate that SGRE has cartilage-protective and anti-inflammatory properties, making it a potential agent for the prevention and treatment of OA. Further clinical studies are being prepared for OA patients[72,102-107].

4.20 *Styphnolobium japonica* L. (*Fabaceae*)

Styphnolobium japonica L. (*Fabaceae*) is also known as the Japanese pagoda tree and Chinese scholar tree. It contains various active phytoconstituents rutin, quercetin, sophoraflavanone G, isoflavonoids, triterpenoids, etc. It has inhibited the induction of osteoarthritis via Compounds such as COX-2, TNF-α, IL-1β, and IL-6 have been examined for their involvement in inflammation. A mixture of 30% ethanol (v/v; 300 L) and 30 kg of *S. japonicum* L. flowers was then extracted by reflux circulation (Sungwon E and C. Uljin, Republic of Korea) for 3 h at 60°C. The extract was then filtered through a 10-25 μm filter. In summary, the results support the anti-arthritic activity, as indicated by the improvement in the weight-bearing index of OA-affected knee joints, the reduction of serum cartilage-degrading enzymes and their derivatives, and a reduction of Mankin's score. Therefore, due to its anti-inflammatory properties, SJFE could be beneficial in alleviating the symptoms of osteoarthritis and has the potential to improve the quality of life for those impacted by the disease. Furthermore, the study also

showed that oral quercetin at 30 mg/kg significantly reduced serum levels of proinflammatory cytokines and the severity score of collagen-induced arthritis in mice. However, in the current study, even at the high dose of SJFE (200 mg/kg), there were still no observable effects of SJFE on TNF-α, IL-1β, or IL-6 on serum levels. The dosage contained free quercetin as well as the quercetin liberated from rutin at a dosage of 36 mg quercetin. The difference would be explained by the fact that the free quercetin amount provided by SJFE was lower than the 30 mg used in the other study. Many studies have evaluated the anti-arthritic activity of other compounds by measuring the expression or levels of proinflammatory proteins in synovial fluid and tissue. If we used joint tissue or fluid for the studies, we may see even greater effects[108-112].

4.21 *Terminalia chebula* (*Combretaceae*)

Terminalia chebula (*Combretaceae*) is also known as Black myrobalan, ink tree, and chebulic myrobalan. Tannins, gallic acid, ellagic acid, cellulitic acid, and ellagic acid are among its active phytoconstituents. It has inhibited the induction of osteoarthritis via AyuFlex®. For a variety of diseases, traditional oriental medicine has made extensive use of an aqueous extract from the fruit *T. chebula*. Its anti-inflammatory and antioxidant qualities have been demonstrated in both preclinical and clinical research. This research explored the potential effects of AyuFlex® on OA, focusing on its impact on interleukin-1 (IL-1)-treated chondrocytes and MIA-induced OA in rats. *In vitro*, AyuFlex® reduced oxidative stress, pro-inflammatory cytokines, and MMPs, while enhancing collagen synthesis. Mechanistically, AyuFlex® inhibited NF-κB and MAPK activation by blocking NF-κB p65 and ERK phosphorylation. *In vivo*, AyuFlex® significantly reduced OA symptoms, including oxidative stress, cartilage damage, and cytokine and MMP changes. These results imply that AyuFlex® might be a useful treatment choice for OA[79,113-115].

4.22 *Upanaha Choornam* (*Upanaha Choornam*) (UC)

Upanaha Choornam (UC), a polyherbal formulation, has shown notable anti-inflammatory properties, with effects similar to the standard drug, Indomethacin. However, its efficacy does not improve with higher doses, indicating an optimal therapeutic concentration. UC is composed of several active phytoconstituents derived from natural ingredients, including turmeric, ginger, eucalyptus, camphor, mustard, aloe vera, pepper, and sandalwood, each known for its medicinal properties. The formulation primarily exerts its effects by targeting key inflammatory pathways, such as NF-κB, COX-2, and LOX. These pathways are critical in the regulation of inflammatory responses, making them important targets for managing conditions like OA. In an experimental study, the use of Swiss Albino mice was evaluated at concentrations of 1000 µg/ml and 500 µg/ml. In both concentrations, a slight upregulation of COX-2 was observed (0.08 and 0.03 folds, respectively) when compared to the control group. UC appeared to have the potential for anti-inflammatory activity through the significant inhibition of important pro-inflammatory mediators such as TNF-α, NO, and COX-2, despite the slight increase in COX-2 expression. By modifying these inflammatory mediators, UC could protect against cartilage degradation and inflammation in OA. These findings suggest that UC could provide a safe and effective, natural treatment for OA, utilising a multi-targeted strategy aimed at either inflammation or joint degeneration[116,117].

4.23 *Veronica incana* (*Plantaginaceae*)

Veronica incana (*Plantaginaceae*), called Speedwell, bird's eye, or gypsy weed, is a medicinal plant known for its rich phytochemical profile. It contains several bioactive compounds, including flavonoids, tannins, saponins, phenolic compounds, and essential oils, contributing to its therapeutic properties. The levels of inflammatory biomarkers, including LOX, TNF-α, IL-1β, and COX-2, are considerably reduced by these compounds. Through these pathways, *V. incana* seems to have potential as an anti-inflammatory agent. In one study, SD rats with OA brought on by MIA were given the crude extract of *V. incana*. The effects of the extract were assessed after it was given at a dose of 200 mg/kg. The findings demonstrated that *V. incana* improved joint health and successfully decreased inflammation. The study also verified that *V. incana* contains four main active components, which are probably what give it its anti-inflammatory properties. According to this study, *V. incana* may be a viable natural remedy for OA, providing a different strategy from traditional

treatments by treating joint degeneration and inflammation at the molecular level[118-122].

4.24 *Tribulus terrestris* (*Zygophyllaceae*) Gokshur

Tribulus terrestris (*Zygophyllaceae*) Gokshur, also known as puncture vine, contains active phytoconstituents such as saponins, flavonoids, alkaloids, tannins, and steroidal saponins. These substances aid in the suppression of inflammatory indicators such as NF-κB, IL-1β, and TNF-α. Two doses of Ethanolic *Tribulus terrestris* (ETT), an extract of Gokshur, were administered to female LEW/SSNHSD rats with MIA-induced OA in a study: 200 mg/kg/day and 400 mg/kg/day. ETT decreased cartilage degradation and bone erosion, according to micro-CT scans. ETT's effects were comparable to those of the COX-2 inhibitor Celebrex. The anti-OA properties of ETT are likely due to its suppression of inflammatory mediators, including NO, NOS2, COX-2, TNF-α, and IL-6. ETT also influenced MMP-2 and MMP-9, which are similar to enzymes that cause cartilage damage. This study shows ETT could be a natural treatment for OA-related inflammation and damage and has potential as a new OA drug[123-127].

4.25 *Cissus quadrangularis* (*Vitaceae*)

Cissus quadrangularis effectively reduces pain in OA patients by suppressing prostaglandin production, molecules linked to pain signaling[128]. *Withania somnifera* significantly decreased complement activity, lymphocyte proliferation, and inflammatory responses in arthritic mice compared to untreated controls[129]. Pro-inflammatory mediators Several pro-inflammatory mediators, including IL-1β, TNF-α, and ROS, have been documented to increase during OA, initiating a cascade effect that leads to the production of cytokines, MMPs and prostaglandins synthesised by chondrocytes[130,131]. *C. quadrangularis* alone, or in combination therapy dose of 100 µg/mL, suppressed the biggest elevations in MMP-3, -9, -12, -13 and PGE2, as well as pro-inflammatory markers IL-1β, IL-18, TNF-α, and PGE2. Similarly, *W. somnifera* reduced the levels of IL-1β, TNF-α, and PGE2. These two medicinal plants demonstrated inhibition of inflammation-related pathways, including NF-κB and MAPK, in association with decreased ERK2 and p38 MAPK. Clinical studies further support the therapeutic potential of these herbs for the treatment of OA, as these natural herbal medications achieve these anti-inflammatory and cartilage regenerative effects by means of inhibiting MMP and ROS. Moreover, surviving seems to play a particularly critical role in the protective aspect of the chondrocyte and osteogenesis by inhibiting p38 MAPK signalling[33,132].

4.26 *Rose Hip* (*Rosaceae*)

Rose hip, derived from *Rosa canina* L., is one of the most widely recognised and popular functional foods globally used for managing OA[133]. Phytochemical characterisations of the rose hip have confirmed the presence of phenolic acids, proanthocyanidins, tannins, flavonoids, fatty acids, pectins, carotenoids, and organic acids[134-137]. The present study used an animal model of OA induced by MIA to assess the chondroprotective and anti-inflammatory effects of a combined Rose Hip Powder (RHP) and Green Tea Seed Extract (GTSE) treatment. Male Wistar rats were used in this study, with a major focus on levels of TNF-α and IL-6. Results indicated the combined chondroprotective effects of RHP and GTSE against MIA-induced OA. Treatment with the RHP-GTSE treatment significantly reduced pain and inflammation levels, with GTSE's anti-inflammatory properties greatly enhanced by the inclusion of RHP. These data indicate the potential of this combination as a therapeutic strategy for OA. In conclusion, the study provides compelling scientific evidence for the use of RHP and GTSE as efficacious therapeutic strategies for OA treatment[138].

4.27 *Morus alba* L. (*Moraceae*)

Morus alba L. (*Moraceae*), commonly referred to as the white berry or mulberry, is a shrub that is indigenous to northern China. In traditional herbal medicine, the root bark, or Sang Bai Pi, of *Morus alba* has been used to expel heat from the lungs, as well as to relieve coughing and wheezing. It has been shown to have several interesting pharmacological effects, such as antibacterial, antiviral, antioxidant, hypoglycemic, hypolipidemic, neuroprotective, antiulcer, analgesic, and anti-inflammatory effects[139-143]. The inhibition of T cells and other immune cells of the MEK/ERK pathway and CXCR-4-mediated chemotaxis may partially account for these effects[144]. The root bark of

Morus alba contains several bioactive compounds, including prenylated flavonoids and stilbenoids, which, in addition to catechol (the major flavonoid in *Uncaria gambir*), may have potential benefits in OA. These compounds act as inhibitors of cyclooxygenase-2 (COX-2), lipoxygenase (5-LOX), platelet phospholipase A2, and pro-inflammatory cytokines, including TNF-α and interleukins (ILs) 1, 2, 6, 8, and 12[140,145]. The climbing shrub *U. gambir* (Rubiaceae), which has rounded branches, has been resourcefully utilised in Asia to support tooth health when accompanied by *Piper beetle* leaves. Extracts made from *U. gambir* are also regularly used in the management of dyspepsia, halitosis, vomiting, and anorexia, as well as diarrhoea and gastritis. The present study investigated UP3005, a standardised formulation containing *U. gambir* leaf extract with *Morus alba* root bark, in the context of a rat model developed by administering MIA to assess additional outcomes in terms of reducing OA symptoms. Six-week-old male Sprague-Dawley rats weighing 160-180 g were used in the experiments. The study revealed that UP3005 reduced inflammation and protected against cartilage degradation, indicating its potential to serve as a natural therapy to relieve OA symptoms and manage the disease itself[146]. It has been demonstrated that Morus alba root bark extract has strong analgesic and anti-inflammatory properties. This extract has shown promise as a medicinal agent for inflammation and pain management. According to studies, these therapeutic effects might be the consequence of altering key inflammatory pathways, offering a natural remedy for a number of conditions, including arthritis, that are linked to persistent pain and inflammation. Further research on the possible therapeutic use of *Morus alba* root bark for pain and inflammation is justified by its pharmacological activity[147]. It lowers the synthesis of IL-6 and NO, two known indicators of inflammation. It might contribute to regulating the entire inflammatory response by preventing the synthesis of these inflammatory chemicals. This is valuable in treating symptomatic conditions characterised by excessive inflammation, such as chronic pain and autoimmune diseases. This information reinforces its usefulness in symptomatic treatment for chronic inflammation, potential inflammation control, and relieving symptoms of various inflammatory diseases[148]. It inhibits the activation of Nuclear Factor kappa B (NF-κB), a key transcription factor that is involved in inflammatory processes. Inhibiting NF-κB activation inhibits the expression of various pro-inflammatory genes, thereby decreasing inflammation and potentially relieving chronic inflammatory disease symptoms. This is particularly important in conditions like arthritis, which have a prominent or major role in the inflammatory process[149]. It also decreases tumour necrosis factor-alpha (TNF-α) levels, a major cytokine in inflammatory processes. By decreasing TNF-α levels, it further suppresses the inflammatory response and may provide relief from conditions where TNF-α has a key role, as in autoimmune disease, chronic inflammatory disorder[150] and IL-1β[151]. This extract is commonly known for its anti-oxidation characteristics[152], ability to scavenge free radicals[153], antiproliferative, cytotoxic[154] and anti-inflammation[155]. A standardised formulation, UP1306, containing an aqueous extract from A. catechu heartwood with an ethanol extract of *M. alba* root bark in a 1:2 weight ratio, was administered daily at 50 mg/kg along with Methotrexate (75 μg/kg) for 3 weeks in a collagen-induced arthritis model. The combined effects of UP1306 in producing reductions in pro-inflammatory cytokines and enzymes responsible for degradation of cartilage matrix suggest its anti-arthritis activity may be, at least in part, mediated through modulation of the immune system[143].

4.28 *Ageratum conyzoides L* (*Asteraceae*)

Ageratum conyzoides L. (*Babandotan* leaves) is a natural product well-known for its anti-inflammatory effects. The anti-inflammatory activity of A. conyzoides has been linked to its ability to inhibit IL-6 signalling. Flavonoid glycosides contained in leaf extracts of A. conyzoides are an important contributor to its anti-inflammatory activity[156,157]. The effect of A. conyzoides on monosodium iodoacetate-induced OA in rats was assessed, with a specific focus on the regulation of TNF-α and MMP-9 expression; both are important mediators of inflammation and proteoglycan breakdown in OA. It was found that babandotan leaf extract significantly reduced OA progression in the sodium iodoacetate model compared to the untreated control group, particularly at 160 mg/200 g body weight[158]. A. conyzoides has low toxicity based on its LD50 properties, which further adds to its safety profile [159]. Treatment with babandotan leaf extract,

which is high in quercetin, significantly reduced TNF-α levels. Quercetin inhibited TNF-α production and gene expression in a dose-dependent manner. Quercetin's anti-inflammatory effect occurs through PBMCs when it inhibits TNF-α cytokine activity by action on NF-κB. The findings of this study show that quercetin-containing babandotan leaf extract can inhibit inflammation and breakdown of proteoglycans by suppressing TNF-α and MMP-9 expression[158].

4.29 *Boswellia serrata* (*Burseraceae*)

The B. serrata tree, native to India, has long been recognised in *Ayurveda* for the therapeutic benefits of its dried resinous gum (guggul), which is known for its anti-inflammatory, anti-arthritic, and pain-relieving effects. Resin is essential for lowering the total white blood cell count in joint fluid, which helps to mend blood vessels that may have been damaged internally or by spam[160]. Pentacyclic and tetracyclic triterpenes contribute the majority of the resin; the former contains boswellic Acids (BAs), which provide the resin its anti-inflammatory effects[161]. BA do not influence prostaglandin synthesis; instead, they inhibit leukotriene production by targeting the 5-lipoxygenase pathway[162]. Anthraquinone derivative Rhein (RH) is a metabolic precursor of diacerein. Pro-inflammatory mediator production is directly inhibited by Rhein[163]. Because rhein contains anti-inflammatory effects and can promote the manufacture of matrix components, diacerein has, in turn, analgesic and function-modifying effects in OA[164,165]. A DSRB, a mutual prodrug of rhein and boswellic acid, was administered orally at a dose of 15.73 mg/kg twice a day. Given that Rhein carries the risk of gastric toxicity, the primary concern was to reduce its ulcerogenic potential, and this endpoint was successfully achieved. DSRB, a prodrug, successfully decreased the ulcer indices linked to diacerein. It proved to be more effective and safer for managing OA compared to their physical combination or the use of individual compounds such as diacerein, rhein, or boswellic acid[166].

4.30 *Caragana sinica* (*Fabaceae*)

Caragana sinica Root (CSR), the certified dried root of *C. sinica* (Buc'hoz) Rehder of the *Fabaceae* family; Caragana genus[167] isolated from Jinhe, Jin Lin, China. CSR is a rich source of bioactive compounds, including (-) α-viniferin, caraganaphenol A, miyabenol C, and kobophenol A (KPA). KPA, as a primary bioactive compound in CSR, has been studied for its ability to promote osteoblast proliferation and anti-inflammatory properties[168,169]. The preventive effects of CSR were evaluated using interleukin (IL)-1β-stimulated rat chondrocytes as well as *in vivo* by using a rat OA model induced by MIA. The anti-inflammatory effects of CSR delay cartilage degeneration by inhibiting inflammatory mediators. Also, CSR demonstrated chondroprotective effects by decreasing the production of catabolic enzymes. The mitogen-activated protein kinases/nuclear factor kappa-light-chain-enhancer of activated B cells (MAPKs/NF-κB) signalling pathway is a key mechanism in OA pathophysiology and a likely therapeutic target that is altered by CSR therapy. CSR presents a potential therapeutic approach for OA by reducing catabolic enzyme production, while allowing anabolic enzymes to be secreted in greater amounts[170].

4.31 *Carya illinoinensis* (*Juglandaceae*)

Carya illinoinensis (Pecans) is are nut-bearing tree predominantly cultivated in the United States, northern Mexico, Australia, and South Africa. Along with phytosterols, tocopherols, and other micronutrients, they are a great source of unsaturated fats, such as monounsaturated and polyunsaturated fatty acids. Beyond their lipid profile, pecans are abundant in bioactive polyphenolic compounds such as epicatechin, tannins, ellagic acid, and gallic acid. They also provide essential vitamins and minerals, including calcium, zinc, magnesium, iron, and phosphorus[171,172]. Pistachios (*Pistacia vera*), native to Asia, have widely spread across Mediterranean regions. They are among the earliest cultivated nuts and are renowned for their richness in antioxidants, attributed to their high levels of phenolic compounds with notable antioxidant potential[173,174].

4.32 *Centella asiatica* (*Apiaceae*)

Centella asiatica, widely recognised as *Gotu kola*, is a significant medicinal herb traditionally useful in Eastern medicine and increasingly valued in Western countries. In addition to improving wound healing, it is used for a range of skin conditions, including psoriasis, lupus, leprosy, varicose ulcers, and eczema. It is also used to treat diarrhoea, fever, amenorrhea,

conditions of the female reproductive system and urinary tract, cognition, and anxiety[175]. *C. asiatica* has also been found to be effective in managing chronic venous insufficiency by improving microcirculation[176]. In a rat model of OA that was induced by tibio-tarsal injection of MIA, a single intra-articular (i.a.) dose of a compound called 14G1862, derived from *C. asiatica* extract, provided significant pain relief for up to two months. The effectiveness of 14G1862, in comparison to a well-established treatment in OA, was triamcinolone acetonide[177]. In RAW 264.7 cells, it has also been shown that 14G1862 significantly inhibited LPS-stimulated production of NO in a concentration-dependent manner and to the same extent as celecoxib (3μM). The extract also displayed dual activity, as it exhibited antioxidant activity by scavenging NO, while also displaying an anti-inflammatory effect by modulating iNOS expression. A single intra-articular (i.a.) injection of 14G1862 was found to significantly reduce hyperalgesia, allodynia, and motor dysfunction in OA; additionally, it restored the NO balance in LPS-stimulated macrophages[178].

4.33 *Zingiber officinale* (*Zingiberaceae*) and *Colocasia esculenta* (*Araceae*)

Zingiber officinale (Ginger) and *Colocasia esculenta* (tubular plant) are commonly recognised as herbal medicinal products for OA treatment. The extract of *Colocasia esculenta* contains bioactive agents such as flavonoids, anthocyanins and mucilage that have a strong anti-inflammatory response[179]. The extract from *C. esculenta* had shown decreased ear oedema thickness in a dermatitis model in rats and prevention of NO in Lipopolysaccharide (LPS) activated RAW 264.7 cells[180]. In this study, twenty-four male Wistar rats were acclimated and randomly assigned into four groups of six rats each, followed by administering an oral gavage of a 90 mg/kg body weight dose of a *Z. officinale* and a *C. esculenta* (CEZO) suspension. MIA was subsequently injected into the knee region and followed up with a massage to ensure the distribution of the solution[181]. The MMP-9, a relevant OA enzyme that is linked to cartilage degradation, was significantly decreased in treatment with CEZO. Pro-inflammatory cytokines expose the elevation of MMP-9 levels, leading to joint deterioration through increased chondrocyte production of MMPs, such as IL-6 and TNF-α[182]. In conclusion, our study indicated that extracts of *Zingiber officinale* rhizome and *C. esculenta* tuber decreased inflammation in a dose-dependent manner by lower concentrations of pro-inflammatory mediators such as TNF-α, IL-6 and NO. Also, in MIA-induced osteoarthritis rats, it decreased cartilage degradation by controlling MMP-9 levels[183].

4.34 *Zingiber officinale* (*Zingiberaceae*)

Zingiber officinale (ginger) is a commonly used kitchen spice renowned for its effectiveness in alleviating nausea during pregnancy, travel-related sickness, and inflammatory disorders such as OA[184]. In IL-1β-induced chondrocyte damage, increased nuclear p65 levels showed that the NF-κB signalling pathway was activated. Treatment with *S*-allylmercaptocysteine-SAMC at low (20 μM) and high (60 μM) concentrations, in conjunction with IL-1β (5 ng/mL), demonstrated that both SAMC and dexamethasone effectively suppressed NF-κB signalling ($P < 0.05$) by promoting cytoplasmic IκBα accumulation and decreasing nuclear p65 levels in a dose-dependent manner. Since type II collagen, the primary structural protein in cartilage, deteriorates during OA progression, its reduction serves as a critical indicator of cartilage degradation. SAMC exerted protective effects by lowering MMP-9 and MMP-13 expression while enhancing TIMP-1 levels, thereby mitigating type II collagen breakdown. Furthermore, NF-κB activation was inhibited and TNF-α expression was decreased, indicating that SAMC may aid in preserving cartilage integrity and protecting chondrocytes in OA[185].

4.35 *Glycyrrhiza glabra* (*Fabaceae*)

Glycyrrhizin, a compound found in liquorice root that belongs to the natural triterpene glycoconjugate category, boasts a wide range of potential pharmacological effects, including antiviral, anti-inflammatory, antitumour, and hepatoprotective effects, and is often prescribed for chronic hepatitis. *Glycyrrhizin* was found to inhibit OA-related biomarkers produced as a result of the pro-inflammatory signalling molecule HMGB1 in knee chondrocytes, including matrix metalloprotease-3 (MMP-3) and MMP-13. It was administered intragastrically at low (20 mg/kg) and high (50 mg/kg) doses after intra-articular MIA injection. The TMJ chondrocytes and disc cells both

have previously shown activated NF-kB pathways, and when the pathway is activated, p65 plays a critical role in the transcription of target genes. Glycyrrhizin has suppressed TLR4 and NF-kB levels in rodents with necrotising enterocolitis, as well as decreased HMGB1, TLR4, IL-1β, and IL-12 levels, as potential protective effects against keratitis. HMGB1 causes inflammation in TMJ OA via the RAGE/TLR4-NF-kB p65/AKT pathway, resulting in elevated release of OA-related factors, whereas glycyrrhizin acts as a protective agent for the condyle against destruction[186-191].

4.36 *Glycine soja (Fabaceae)*

Glycine soja (GS), the wild progenitor of the cultivated soybean, has been utilised in China for more than 2000 years and is regarded as an important source of medicinal compounds derived from soybeans. Known for its rich bioactive components, Traditional Chinese medicine has continuously recognised GS for its therapeutic properties, contributing to its use in various treatments. The plant contains several compounds that possess antioxidant, anti-inflammatory, and immune-modulating effects, which have made it a valuable resource for the development of natural remedies[192]. The leaf extract of *Glycine soja* (GSLS) exhibited anti-inflammatory properties and prevented Extracellular Matrix (ECM) degradation by downregulating MMP-1, MMP-3, and MMP-13 by inhibiting the NF-κB signalling pathway in IL-1β-stimulated SW1353 cells. GSLS significantly reduced inflammatory markers in chondrocytes and reduced pain and cartilage damage in MIA-induced osteoarthritis rats. At 200 μg/mL, GSLS significantly suppressed the expression of PGE2, IL-1β, and IL-6. Overall, the findings suggest that GSLS decreases inflammation in chondrocytes and may delay cartilage degeneration by inhibiting subsequent activation of the NF-κB pathway in SW1353 cells[193].

4.37 Grape seed (*Vitaceae*)

Grape seed is mostly known for its rich array of antioxidant compounds, including oligomeric proanthocyanidins and catechins, and its notable anti-inflammatory properties, making it a favored option for managing OA[194,195]. Research has demonstrated that orally administered grape seed extract in OA rat models helps prevent chondrocyte and proteoglycan loss, inhibits osteophyte development, and reduces ROS (reactive oxygen species) and inflammatory mediators like MMP-13, nitrotyrosine, and IL-1β. The therapeutic effects of grape seed oil are primarily mediated through the COX-2 and NF-κB signalling pathways. However, the full range of factors contributing to OA in humans is not yet completely understood, and the biomechanical functioning of the knee varies significantly between rodents and humans. Few *in vivo* studies have indicated that grape seed oil has a number of health benefits for people, such as anti-inflammatory, anti-cancer, cardioprotective, and antibacterial properties[196-198]. Furthermore, a combination of grape seed oil and avocado was found to be as effective as Piascledine (a formulation of avocado and soybean), indicating the potential for modifying or substituting the components of conventional treatments[197].

4.38 *Psidium guajava* L. (*Myrtaceae*)

Psidium guajava L. (fruit and leaves of the Gola guava tree), which is part of the *Myrtaceae* family, contain a variety of bioactive compounds, including vitamin C, syringic acid, gallic acid, kaempferol, ellagic acid, quercetin, chlorogenic acid, ferulic acid, ascorbic acid, and m- and p-coumaric acids[199]. These phytochemicals provide excellent anti-inflammatory and antioxidant effects, which can decrease ROS levels and downregulate pro-inflammatory cytokines expression in chondrocytes, cartilage explants, and animal models of OA[200]. In this article, a 4% papain and 0.03 M cysteine solution were reconstituted using distilled water to create an osteoarthritis model in rodents[201], targeting not only TNF-α, IL-1β, IL-6, and COX-2, but also other related pro-inflammatory signalling pathways. The anti-inflammatory and immunomodulatory effects of 50% hydroethanolic extracts of both white Gola guava fruit (GF50%) and guava leaves (GL50%) at various doses were measured in a papain-induced osteoarthritis model using Sprague-Dawley rats. In particular, the GL50% extract demonstrated chondroprotective effects at the highest dose (400 mg/kg), explaining this protective effect through modulation of cyclooxygenase-2 (COX-2) and key pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), along with maintaining the corresponding oxidative and antioxidant markers indicating a state of oxidative stress without negatively impacting liver and kidney function[202,203].

4.39 *Rosmarinus officinalis* L. (*Lamiaceae*)

Rosmarinus officinalis L. (*Rosemary*) has been utilised for years to treat diseases such as dysmenorrhea, asthma, and renal colic, and rosemary essential oil is composed of a high proportion of monoterpenes that exhibit anti-inflammatory, antioxidant, and anti-nociceptive effects. The best emulsifier ratio to produce nano-emulsions is 1:1:3 in the order of cruder, Tween 20, and Tween 80. The analgesic activity of the nano-emulsions was investigated in an intra-articular model of osteoarthritis induced by MIA. In previous studies, it was shown that MIA injections could induce chondrocyte apoptosis. Moreover, while it can cause superficial fibrillation and deep cracks in the cartilage, it has been shown that rosemary can relieve joint inflammation and degeneration of articular cartilage. It has been shown that rosemary essential oil reduces the inflammatory exudate count and number of migrating cells eight hours after carrageenan-induced inflammation in rats. Overall, these findings suggest that the therapeutic properties of rosemary and peppermint essential oils may be useful in the treatment of osteoarthritis, especially if applied topically[204-208] and mixture of *R. officinalis* (*Lamiaceae*) and *Populus alba* (*Salicaceae*), commonly known as rosemary and white poplar, respectively, contain various bioactive constituents, including rosmarinic acid, carnosic acid, carnosol, 1,8-cineole, salicylates, quercetin, phenolic acids, and tannins. These compounds exert their effects through pathways such as COX-2 and NF-κB. In this study, Wistar rats with MIA-induced knee osteoarthritis were treated with Essential Oils (EO) derived from the leaves and flowers of *R. officinalis* and *P. alba*. Radiographic and histological Analyses were performed to assess the essential oils' medicinal effectiveness. The results demonstrated that the EOs significantly decreased the Mankin score contrast to the untreated group, indicating a protective or potential effect against osteoarthritis, albeit with varying degrees of effectiveness[209].

4.40 *Schisandra chinensis* (*Schisandraceae*)

Schisandra chinensis (*Schisandraceae*), also known as Magnolia vine, Five-flavour berry. It contains various bioactive constituents: Triterpenoids, Lignans, Flavonoids, Polysaccharides, Phenolic Compounds, and Essential Oils[210]. IL-1β activates transcription factors via the MAPK and NF-κB pathway [211]. This study showed that *S. chinensis* Leaf Extract- SCLE had anti-inflammatory properties in male Sprague-Dawley rats with MIA-induced OA and RAW 264.7 cells caused by LPS. Kaempferol and quercetin, the primary active compounds in SCLE, were highlighted for their therapeutic properties. The results showed that SCLE effectively alleviates pain and reverses degeneration of cartilage by suppressing inflammatory properties. According to these results, SCLE may be a good option for treating OA patients' pain and inflammation. To determine which active components in SCLE are responsible for its therapeutic properties, as well as to investigate their modes of action and the related signalling pathways, more research is necessary[210].

4.41 *Scoparia dulcis* (*Plantaginaceae*)

Scoparia dulcis (*Plantaginaceae*), commonly known as licorice weed or goat weed, includes active ingredients that contribute to the inflammatory and nociceptive processessuch as flavonoids, terpenes, tannins, saponins, and steroids[212-214]. In a study utilising BV2 microglial cells treated with lipopolysaccharides, it was shown that the plant's crude extract inhibited pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, NO, and PGE2. These actions were based on downregulation of the NF-κB, JAK-STAT, and p38 MAPK signalling pathways, while signalling via the Nrf2/HO-1 pathway was upregulated[215]. A study of Wistar rats with MIA-induced OA showed that after oral administration of a total extract of *S. dulcis*, a significant reduction in oedema, spontaneous pain, and peripheral nociceptive activity was observed, in addition to reduced synovial concentrations of IL-6 and IFN-γ and a significant increase in IL-10. A reduction in histological changes in articular cartilage and synovial membranes was also noted, which is indicative of the extract's anti-inflammatory activity. Crude extract administration at a 50 μg/mL concentration resulted in the greatest activity inhibition of COX-1 and COX-2 in the studied extract. The experimental compounds also determined suspensive and nicotiflorin that showed a substantial binding affinity with the presented COX-2 structure and interact with important residues in the COX active site, as well as neighbouring residues including Arg120 and Glu524[216].

4.42 *Ziziphus jujuba* (*Rhamnaceae*)

Ziziphus jujuba (*Rhamnaceae*), commonly known as jujube, contains various active constituents such as flavonoids, polysaccharides, polyphenols, terpenoids, saponins, and nucleotides[217,218]. These compounds have been shown to significantly inhibit this study showed that SCLE had anti-inflammatory properties in male Sprague-Dawley rats with MIA-induced OA and LPS-induced RAW 264.7 cells. Kaempferol and quercetin, the primary active compounds in SCLE, were highlighted for their therapeutic properties. The findings demonstrated that by inhibiting inflammatory reactions, SCLE successfully reduces pain and stops cartilage deterioration. These discoveries suggest that SCLE could be a promising approach to determine which active components in SCLE are responsible for its therapeutic effects, as well as to investigate their modes of action and the related signalling pathways, more research is necessary. Conventional treatments, such as celecoxib, for managing OA progression and symptoms[219].

4.43 *Dashmoolarishta*

This traditional Ayurvedic polyherbal composition utilises roots from ten different plants, such as *Aegle marmelos, Oroxylum indicum, Stereospermum suaveolens, Premna integrifolia, Gmelina arborea, Solanum xanthocarpum, Solanum indicum, Desmodium gangeticum, Uraria logophiles, and Tribulus Terrestris*[220]. Mice were subjected to OA induction through MIA, which inhibits glyceraldehyde-3-phosphate dehydrogenase, leading to articular cartilage degradation and OA changes. The formulation inhibited NF-κB, a key factor in the progression of OA[221]. Thirty-five Swiss albino mice (20–30 g, both sexes; inbred strains) were randomly chosen for the investigation. *Dashmoolarishta* (high-dose or HD and low-dose or LD) treatments led to significant improvements in pain (based on behavioural analysis), along with significant reductions in joint damage (knee joint histopathological data). *Dashmoolarishta* produced a significant reduction in pain, knee joint swelling, and histopathological scores due to its apparent analgesic, anti-inflammatory, and anti-arthritic effects[222,223].

4.44 *Eucommia ulmoides* (*Eucommiaceae*)

In China, Japan, Korea, and other regions as a medicinal tonic[224]. The aqueous extract from the bark of *Eucommia ulmoides* (EUE) protects the articular cartilage in rats[225]. In the current study, rats in Group C received orally an EUE dose of 1.35 g/kg/day, while another group received a dose of 2.70 g/kg/day. The EU possessed anti-inflammatory properties by inhibiting the synthesis of TNF-α and IL-6, along with reduced release of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages. The EUE also reduced the levels of matrix metalloproteinase-3 (MMP-3) in the articular cartilage, which MMP-3 may support cartilage degeneration. EUE also inhibited phosphorylation of the Akt protein and effectively blocked the PI3K/Akt signalling pathway. The findings presented indicate EUE possesses anti-OA potential and is capable of preventing OA progression by reducing pro-inflammatory cytokines, MMP-3 levels, and inhibiting the PI3K/Akt signalling pathway[226,227].

4.45 *Lawsonia inermis* L. (*Lythraceae*)

Lawsonia inermis L. (*Lythraceae*) is noted to have anti-inflammatory, analgesic (pain-relieving), and antipyretic (fever-reducing) actions[228]. It contains natural components such as lawson (2-hydroxy-1,4-naphthoquinone), mucilage, essential oils, tannins, gallic acid, lipids, glucose, mannitol, and resin[229]. Traditionally, *Ricinus communis* L. (*Euphorbiaceae*) has been used to treat gout, oedema conditions, and skin disorders[230]. Furthermore, this plant is rich in polyphenols and flavonoids, which have potent anti-inflammatory and antioxidant effects[231]. The main study was conducted to investigate the anti-inflammatory and analgesic effects of a topical preparation using extracts of *L inermis* and *R communis* based on the information collected from traditional Iranian medicine. To find out the anti-inflammatory potential of the topical preparation to reduce knee pain, we induced osteoarthritis in 36 male Wistar rats by injecting MIA. Mechanistically, the treatment worked via the NF-kB signalling pathway. The results showed that topical administration of the mixture of *L. inermis* and *R. communis* extract effectively reduced pain and inflammation while also mitigating the effects of MIA-induced osteoarthritis pain. The study confirmed the efficacy of treating MIA-induced osteoarthritis pain and inflammation via topical application of a mixture of extracts, with purported mechanisms of action

through anti-inflammatory and analgesic activity through several assessments[232].

4.46 *Andrographis paniculata* (*Acanthaceae*)

Andrographis paniculata (*Acanthaceae*) is also called the king of bitters, which is commonly used in treating gastrointestinal tract, fever, sore throat and upper respiratory infections, analgesic, antibacterial, antiviral and hepatoprotective. The main phytoconstituents like andrographolide, Neoandrographolide, Deoxyandrographolide, andrographan, andrographiside, andrographon[233-235]. These compounds have been shown to significantly inhibit this study showed that *Andrographis paniculata* had anti-inflammatory properties in male SD rats with MIA-induced osteoarthritis. APE decreased OA-induced cartilage degradation and enhanced weight-bearing in the hind limbs. It decreased the levels of matrix metalloproteinases (MMP-1, MMP-3, MMP-8, and MMP-13) and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) in the blood. APE decreased mice's acetic acid-induced writhing in pain models. It decreased the expression of IL-1β, IL-6, COX-2, and iNOS in LPS-stimulated RAW 264.7 cells and inhibited the generation of nitric oxide *in vitro*. These findings suggest that APE may be used to treat OA as an analgesic and anti-inflammatory activity[236,237].

4.47 *Alpinia oxyphylla* (*Zingiberaceae*)

Alpinia oxyphylla (*Zingiberaceae*) has been used for centuries in China for food and medicinal substances. It is one of the four famous southern medicines in China. It contains the main phytoconstituents Tectochrysin, Izalpinin, Chrysin, Kaempferide, Yakuchinone A and B, Oxyphyllacinol and phenols. It is widely used to treat hyperuricemic, inflammation, diarrhoea, hypertension, tumours, and cerebrovascular disorders[238-240]. According to the study, both *in vitro* and *in vivo*, AOE (extract) exhibits potent anti-inflammatory and anti-osteoarthritis properties. AOE (100 μg/ml) significantly decreased NO, PGE_2, IL-1β, IL-6, and TNF-α production in LPS-stimulated RAW 264.7 cells while also blocking ERK, JNK, and p38 MAPK activation. In the rat model of OA caused by MIA, oral AOE (150 or 300 mg/kg) reduced pro-inflammatory cytokine and mediator levels, avoided cartilage deterioration, and reduced joint discomfort. These results imply that AOE, which targets MAPK-mediated inflammatory pathways, is a promising treatment option for osteoarthritis[241,242].

4.48 *Cynanchum wilfordii* (*Asclepiadacease*)

Cynanchum wilfordii (*Asclepiadacease*) roots that is used in traditional medicine in Korea. It dried roots of *Cynanchum wilfordii* are called Baeksuo in Korea. It is widely revealed that various medicinal effects of these plants are particularly anti-inflammatory, anti-oxidative effects and reduction of depression and antineoplastic symptoms. Main phytoconstituents β-sitosterol, auriculosides I-IV, cynanauriculosides I and II, haneoekinols, quercetin, tamarixetin and and other constituents including cinnamic acid, sinapic acid[243-245]. Cynandione A is a major active ingredient in *C. wilfordii* Aqueous Extract-CPAE, which is mostly derived from the plant *Cynanchum wilfordii* (C.W.). Without inducing cytotoxicity, cynandione A and C.W. root extract both dramatically lower concentration-dependent Lipopolysaccharide (LPS)-induced NO generation and inducible nitric oxide synthase (iNOS) expression. It has also been observed that C.W. extract inhibits the production of NF-κB, a key mediator of inflammation. Its anti-inflammatory and anti-osteoarthritic properties are believed to be attributed to phenolic chemicals, specifically p-hydroxyacetophenone and cynandione A[246,247].

4.49 *Litsea japonica* (*Lauraceae*)

Litsea japonica (*Lauraceae*) fruits are mostly distributed in Korea and South Asian regions. Traditional medicine used in folk medicine is limited. Main constituents like Germacrene D, caryophyllene, akolactones A, B, D and E, hamabiwalactones A and B, lincomolide C, litsealactones A and B. Biological studies have shown the potential effects as an anti-inflammatory, anti-complement and antidiabetic properties and are prospective therapies for diabetic retinopathy, osteoarthritis and analgesic[248-250]. The preventive properties of a 70% ethanolic extract of *L. japonica* fruit were assessed in a rat model of osteoarthritis caused by MIA. Tibial subchondral bone structure was enhanced by LJFE treatment (100–200 mg/kg), which decreased the frequency of aberrant bone objects while improving bone volume and cross-sectional thickness. In comparison to OA controls, it also achieved over

80% inhibition of MMPs and Tissue Inhibitors of Metalloproteinases (TIMPs), and it markedly decreased the expression of inflammatory cytokines. According to these results, *L. japonica* fruit extract is a promising anti-osteoarthritic drug since it helps maintain cartilage integrity, control inflammation, and prevent matrix breakdown[251].

5. Discussion

Osteoarthritis (OA) is driven by a multifaceted network of factors, including mechanical stress, persistent inflammation, oxidative damage, and progressive degradation of the cartilage matrix. This review illustrates how various medicinal plants can intervene at multiple points in this complex disease process. Botanicals such as *Curcuma longa*, *Boswellia serrata*, *Vitex negundo*, and *Crataegus sinica* have shown significant promise in downregulating key inflammatory pathways like NF-κB and MAPK, thereby reducing the production of pro-inflammatory cytokines and enzymes such as MMPs and ADAMTS that contribute to cartilage breakdown. The advantages of mixing several plant extracts are highlighted by polyherbal preparations, such as Dashmoolarishta and Upanaha Choornam, which provide a wider therapeutic range. In preclinical animals, these formulations have shown chondroprotective and pain-relieving properties; their effectiveness is frequently on par with that of conventional NSAIDs, but they have fewer adverse effects. The synergistic potential of phytotherapy in controlling OA is shown by its capacity to target various molecular pathways. Lesser-known targets, including the JAK/STAT and AMPK pathways, which are involved in immune regulation and energy balance within joint tissues, are also being suggested by emerging data. These signalling pathways seem to be influenced by natural substances like harmine and astragaloside, which may have a function in disease modification beyond symptom management. Traditional applications offer a solid basis, but scientific verification is still essential. Transforming these plant-based treatments into common clinical practice will require standardising dosages, improving bioavailability, and carrying out thorough clinical trials. Phytomedicine may be useful in increasing the therapeutic options for OA as interest in integrative therapies develops, especially for patients looking for longer-lasting, safer alternatives.

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7. Author Contribution

K.J.P, A.B.S, R.W: Conceptualisation; H.S, A.N: Collection of literature, Data mining; K.J.P, H.S, A.N: Writing-original draft preparation; A.B.S, A.N: Writing-review and editing. All authors have read and agreed to the published version of the manuscript.

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