Potential of Phytomolecules in sync with nanotechnology to surmount the limitations of current treatment options in the management of osteoarthritis

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ABSTRACT

Osteoarthritis (OA), a chronic degenerative musculoskeletal disorder, progressively increases with old age. It is characterized by progressive loss of hyaline cartilage followed by subchondral bone remodelling and inflammaging. To counteract the inflammation, synovium pours various inflammatory and immune mediators along with metabolic intermediates which further worsen the condition. However, even after recognizing the key molecular and cellular factors involved in the progression of OA, only disease-modifying therapies are available such as oral and topical NSAIDs (Non-steroidal anti-inflammatory drugs), Opioids, SNRIs (Serotonin-norepinephrine reuptake inhibitors), etc addressing symptomatic treatment and functional improvement in lieu of suppressing OA progression. Long term use of these therapies leads to various life-threatening complications. Interestingly, mother nature has numerous medicinal plants containing active phytochemicals that can act on various targets involved in the development and progression of OA. Phytochemicals have been used for millennia in traditional herbalism and are promising alternatives with a lower rate of adverse events and efficiency frequently comparable to synthetic molecules. Nevertheless, their mechanism of action in many cases are elusive and/or uncertain. Even though many *in vitro* and *in vivo* studies show promising results, clinical evidence is scarce. Studies suggests that, presence of carbonyl group at 2nd, chloro at 6th along with electron withdrawing group at the 7th position exhibited enhanced COX-2 (Cyclo-oxygenase-2) inhibition activity in OA. On the other hand, the presence of a double bond at C_2-C_3 position of C ring in flavonoids plays an important role in Nrf_2 activation. Moreover, with the advancements in the understanding of OA progression, SARs (Structure activity relationships) of phytochemicals and integration with nanotechnology have given great opportunities to develop phytopharmaceuticals. Therefore, in the present review, we have discussed various promising phytomolecules, SAR as well as their nano-based delivery systems for the treatment of OA to motivate the future investigation of phytochemical based drug therapy.

Key words: Phytochemicals, Osteoarthritis, Phytopharmaceuticals, Natural products, Structure-activity relationship, Topical delivery, Antioxidants, Anti-inflammatory

1. INTRODUCTION

Osteoarthritis (OA) is a mechanised disabling, degeneration of bone in patients with a higher age group. It occurs due to ageing, mechanical stress on joints, and inflammation [1]. OA accounts for 2-3% of morbidity and is estimated to affect approximately 300 million people around the world [2]. As per WHO (World Health Organization) reports about 9.6% of men and 18% of women aged over 60 have symptomatic OA. The development of OA restricts the day-to-day activity in 80% of patients, whereas 25% of patients depend on their wards. Among people over the age of 70 years, 40% suffer from knee OA [3]. The estimated healthcare cost for 27 million patients diagnosed with OA in the USA is approximately US$185.5 billion/year or more profoundly US$6870/patient. The average total annual cost of OA per patient is similar in Europe, ranging from €1330 to 10,452. The total economic burden of arthritic diseases falls between 1-2.5% of developed countries gross national product (GNP) [4].

Previously, it was thought of as a disease of articular cartilage. However, the latest research findings proved that OA condition involves inflammation in the entire joint. Primarily, the loss of articular cartilage encounters a combination of cellular changes and biochemical stress. This leads to subchondral bone remodelling, development of osteophytes, progression of bone marrow lesions, modifications in synovium joint capsule, ligaments, periarticular muscles and meniscal tears with extrusion. OA can transpire in any synovial joint, but it is predominantly observed in the knee, hip, hand, and facet joints of spines. The probability of precipitation of OA is increased post occurrence of any injury, obesity, and hormonal imbalance [5]. The diagnosis of OA is usually carried out with clinical and radiological tools. In the case of geriatric patients, OA is confirmed by crepitus and pain, whereas radiographical data is required to differentiate it from conditions like rheumatoid arthritis. Radiographical data helps in the detection of joint space narrowing and the development of osteophytes. Globally, arthritis is one of the most prevalent disabilities and morbid types of disorder.

To date, none of the structure modulating therapy or treatment has been approved by the regulatory bodies around the world. Presently, many pain-relieving agents are available in the market however their usage is restricted due to associated side effects. There are some candidates, which can detect OA in the early stage by detecting the presence of various biomarkers and prevent irreversible joint damage. Imaging biomarkers for early detection of OA in combination with tissue engineering approaches can become one of the preventive measures [6]. Complexities involved in the development of OA makes the single therapy ineffective against it. Therefore, to attain better results strategies should include symptomatic as well as structure modifying therapies.

In recent years, the use of phytogenic compounds has increased [7,8] phytogenic compounds have natural growth promoting characteristics [9,10]. One of the alternatives to antibiotics, as natural antimicrobial growth promoters is the use of phytobiotics and medicinal plants [9]. The replacement of phytogenic compounds (phytobiotics and medicinal plants), including the essential oils, alkaloids, and flavonoids, has many benefits, including prevention of particular diseases [7], increasing antimicrobial and antioxidants functions [8], progression of liver activities [11]improvement of enzymes related to digestion [10] rising zootechnical yield criterions, and hypocholesterolemic effects [12]. In most of the countries, the use of phytochemical based pharmaceuticals is unestablished due to a lack of clinical data. To consider phytomolecules as established drug molecules, more research and regulatory requirements should be taken under consideration. Hence, the present review is an attempt to portray the possible sites for drug targeting, multifarious promising phytochemical ligands with their structure-

activity relationships (SARs), barriers in the use of phytomolecules and the application of nano drug delivery systems in the development of phytopharmaceuticals for the management of OA.

2. ETIOLOGY OF OA GENESIS

Traditionally OA was considered as a 'wear and tear' disease that progresses with age. Research studies indicated that the pathogenesis of OA involves cartilage degradation and bone remodelling due to active chondrocyte response in articular cartilage and the presence of inflammatory cells in nearby tissues [13]. The upregulated release of enzymes from inflammatory cells results in the destruction of collagen, proteoglycans as well as articular cartilage. The underlying subchondral bone on exposure causes sclerosis trailed by reactive modifying changes that trigger the formation of osteophytes and subchondral bone cysts. As the disease progresses joint space is lost and results in 'wear and tear' process [14]. The development of OA is a multifactorial process and can be caused by primary factors such as obesity, advancing age, sex and sex hormones, genetic makeup, and manual labour, whereas secondary factors involve trauma and diseases related to connective tissues [15]. Even though epidemiological research studies have helped us to understand the risk factors responsible for the precipitation of OA, but still comprehensive research is required to understand the initiating events that trigger the disease.

There are a number of causative mechanisms and various interrelated biochemical, mechanical, and immunological actions that results in the degradation of articular cartilage [5]. The bones of synovial joints in a healthy person are comprised of a thin layer of hyaline cartilage covering that reduces friction and promotes even distribution of force on the bones [16]. The cartilage comprises specialized cells known as chondrocytes, which generates large amounts of collagenous extracellular matrix which includes proteoglycans for compressive strength and collagen fibers mainly type II to provide tensile strength [17]. Earlier development of OA results in the increase of cartilage water content whereas the concentration of proteoglycans falls [18]. The subsequent development of OA leads to microfractures in cartilage and cartilage breakdown products that cause synovitis and upswings the immune response [19].

In response to inflammation in the synovial membrane, the synovium starts to pour inflammatory mediators, mainly cytokines, at the site of inflammation. The presence of cytokines activates the chondrocytes which produces a variety of immune mediators and metabolic intermediates such as tumour necrosis factor-α (TNF-α), interleukin 1β (IL-1β), interleukin-6 (IL-6), nitric oxide (NO), prostaglandin E_2 (PGE_2) and matrix metalloproteinases (MMP) that stimulate the catabolic process in the cartilage and causes structural changes [19,20]. Nearly every OA patient is detected with upregulated production of inflammatory mediators. The overexpression of A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) and aggrecan degradation molecules is responsible for the cartilage damage that later confirmed by stimulating IL-1β in OA chondrocyte and synovial fibroblast [21,22]. IL-1β is also involved in the suppression of the anabolic process in cartilage by downregulating the expression of extracellular matrix such as aggrecan and type II collagen [23]. TNF-α is a pleiotropic cytokine that acts as a proinflammatory factor as well as an immunosuppressive mediator. TNF-α also causes catabolism in cartilage similar to IL-1β by inducing overexpression of MMPs in chondrocytes [24]. The active chondrocytes in osteoarthritic joints produces different types of MMPs such as collagenase (MMP-1, MMP-8, MMP-13, MMP-18), gelatinases (MMP-2, MMP-9) and membrane-type MMPs (MT-MMPs:

MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-25) [25]. Among these, MMP-1, MMP-8, and MMP-13, and MT-MMP-14 acts as a key player in the destruction of collagen. The most important factor for collagen destruction was found to be MMP-13, since it has a substrate preference for type II collagen [26]. Apart from this, the role of infrapatellar fat, substance P, leptin, hypoxia-inducible factor (HIF)-1 and 2-α, mitogen-activated protein kinases (MAPKs), and other proinflammatory factors in the development of OA are under probation [27,28]. Even after recognizing so many molecular and cellular factors involved in the progression of OA, still there is no single molecule available or developed which can prevent or reverse the destruction of cartilage and stop the worsening of the condition.

3. EXISTING PHARMACOLOGICAL THERAPIES FOR OSTEOARTHRITIS MANAGEMENT AND THEIR INADEQUACIES

Current treatment options for OA include the use of topical and oral NSAIDs (Non-steroidal anti-inflammatory drugs), opioid analgesics, serotonin-norepinephrine reuptake inhibitors (SNRIs) and intra-articular injections of corticosteroids and hyaluronic acid (HA) for symptomatic relief from pain. However, still there is no treatment available having structure-modifying ability [27,28].

NSAIDs are an affordable treatment option all around the world for the management of OA. NSAIDs provide relief from pain by inhibiting cyclo-oxygenase (COX) enzymes and increasing mobility [29]. COX enzymes are present in 2 isoforms: COX-1 is constitutively expressed or famously explained as a housekeeping enzyme and actively participates in the maintenance of normal physiological functions of stomach lining, whereas COX-2 is an inducible form, mainly overexpress by cytokines and inflammatory stimuli [30]. Most of the currently used NSAIDs are nonselective COX inhibitors, which gives multiple gastric related side effects like dyspepsia, peptic ulcer, haemorrhage, and perforation. The chances of upper gastrointestinal bleeding associated with NSAIDs have been estimated at 1-2.5/100 people every year [31]. Although few selective COX-2 inhibitors such as meloxicam, celecoxib, rofecoxib, valdecoxib are available for the treatment of OA, however; there uses are very limited due to their high cost [32,33]. As per Osteoarthritis Research Society International (OARSI) recommendations, NSAIDs should be used at a minimum effective dose for a short duration.

Opioid analgesics are used for the management of moderate to severe pain, in case of failure or contraindication of NSAIDs [34]. The use of an opioid analgesic (tramadol) is increasing in the treatment of OA. However, the occurrence of side effects associated with opioid analgesics dwarfs their benefits [35,36]. Other than this, opioid analgesics must be administered at lower effective doses as well as their regular use should be circumvented.

SNRIs are a group of antidepressant drugs principally used for the management of major depressive disorder and other mood-related disorders. However, in 2010, FDA approved the use of duloxetine hydrochloride for the treatment of chronic musculoskeletal pain. Various randomized clinical trials conducted to evaluate the efficacy of duloxetine hydrochloride in the management OA. Therefore, additional studies are required for the establishment of optimal dosage, long-term efficacy, and safety of patients [37]. Apart from this, SNRIs exhibit many side effects like suicidal thoughts and behaviour, hepatotoxicity, serotonin syndrome, seizures, urinary retention, etc. which limits their utility in pain management.

Intra-articular injections of corticosteroids and HA are selectively used for the management of moderate to severe pain conditions in OA patients. HA concentration in healthy synovial fluid was found to be 2.5-4 mg/mL, whereas in an arthritic synovial fluid, HA tumbles down to 0.33-1.5 mg/mL [38]. Therefore, intra-articular injection is recommended in the management of OA to elevate the HA concentration. The use of intra-articular HA has been relegated due to its efficacy variability. However, to mitigate the prognosis of OA disorder, plant-based phytopharmaceuticals are the best therapeutics.

4. PHYTOMOLECULES IN THE MANAGEMENT OF OSTEOARTHRITIS

Presently, there is no pharmacotherapy available that can effectively restore the original structure and function of cartilage and synovial tissues. Therefore, there is an urgent need to have an alternative treatment option for the management of chronic arthritic conditions. A multiple number of phytopharmaceuticals are available as solid, semisolid, and liquid dosage forms for the management of arthritic conditions. **Table 1** summarizes the currently available phytopharmaceuticals used in the management of arthritic conditions.

Table 1: Plant-based marketed formulations for management of arthritic conditions.

Product name	**Biological sources**	**Dosage forms**	**Manufacturers**
Mahanarayana tel	Aegle marmelos Withania somnifera Solanum indicum	Oil	Baidyanath group
Arthrella	Piper betel Ricinus communis Boswellia serrata Vitex negundo Oroxylum indicum Cyperus rotundus Zingiber officinale Strychnos nux-vomica Hyoscyamus niger	Tablet Oil Ointment Cream	Charak pharma
Rumaxel	Gaultheria fragrantissima Pinus roxburghii Eucalyptus globules Mentha arvensis	Gel	Trio Healthcare private Limited
Fine joint	Boswellia serrata Curcuma longa Bromelain extract	Tablet	Aurora Nutraceuticals Pvt Ltd
Muscle and joint rub	Ricinus communis	Cream	Himalaya
Sensur Rub	Mentha piperita Cinnamomum camphora Eucalyptus globulus Eugenia caryophyllus Cinnamomum zeylanicum	Ointment	Integrace Pvt Ltd

Drugs obtained from plant source exhibit multiple special features such as higher molecular mass, a larger number of SP^3 hybridized carbons, a higher number of H-bond acceptors, and donors associated with a lesser number of nitrogen and halogen atoms [39-41]. Despite having multiple advantages over synthetic molecules, plant-derived medications are considered as Complementary and Alternative Medicine (CAM) or nutraceuticals. Plant-based medicines are made by amalgamation of one or more plant extracts which causes difficulty in purity detection. Apart from this, the proportion of active chemicals in plant extract varies depending upon genetics, time of

harvesting, method of drying, method of processing, and other miscellaneous factors [42]. Therefore, phytopharmaceuticals can be scale-up using purified phytochemicals to increase the potency as well as ease of the quantification process during quality control and assurance. All these measures can result in the usage of phytomolecules as active pharmaceutical ingredients.

Phytochemicals obtained from plant sources can be classified into primary metabolites and secondary metabolites. Primary metabolites mainly consist of chemicals that are essential for the growth and development of plants, such as nucleic acids, amino acids, fats, carbohydrates [43]. Secondary metabolites are produced by plant cells to resist the attack of bacteria, fungi, viruses, as well as animals [44]. Primary metabolites are synthesized by plant cells for regular biological functions, whereas secondary metabolites are produced by modifying primary metabolism pathways depending upon the secondary metabolite requirements [45]. Mother nature is filled with plenty of secondary metabolites, out of which alkaloids, glycosides, coumarins, essential oils, steroids are primarily used in the management of various chronic disorders.

4.1. Alkaloids

Alkaloid is a term used to describe a group of vast numbers of naturally produced compounds exhibiting alkali-like properties and contains one or more nitrogen in their heterocyclic ring structure [46]. Generally, alkaloids are alkaline in nature but very few exhibit neutral or slightly acidic characteristics. Alkaloids are secondary metabolic compounds derived from amino acids by plants as well as a few animals. Alkaloids display diverse activities such as anti-inflammatory, analgesic, anti-cancer, antimicrobial, antifungal, local anaesthetic effects, neuropharmacological action and many more. The alkaloidal drugs having therapeutic activity against OA mainly exhibit COX enzymes inhibition [47–58], MMP proliferation [59–65] and modulation of cytokines as well as pro-inflammatory factors [66–68]are represented in Table 2, Table 3, and Table 4, respectively.

4.2. Coumarins

Coumarins are naturally occurring phenolic substances in plants, produced via metabolic processes. Coumarins display anti-inflammatory and antioxidant activity due to which they provide beneficial effects in a range of conditions such as cancer, inflammation, arthritis, burn, and cardiovascular disorders. Apart from this, coumarins act on a diverse group of enzymes and receptors such as COX enzymes [69–86](**Table 2**) as well as TNF-α, IL's, [87–90] involved in the progression of inflammation and deterioration of cartilage (**Table 4**). Researchers found out that coumarin scaffolds can be used for the preparation of synthetic coumarin analogues having better therapeutic efficacy and pharmacokinetic profile. To enhance the activity of coumarins in the management of OA, many substitutions are found to be useful [91]. Existence of oxygen in the coumarin scaffold is essential for specific binding to COX-2 enzyme and it is assisted by the presence of a heterocycle ring containing a nitrogen atom. On the other hand, substitution at 7th position with nitrogen-containing heterocyclic rings such as pyridine amplifies the anti-inflammatory activity, whereas swapping it with a phenyl ring exhibited a contradictory effect. Substitution of chloro group at the 6th position preserved the activity whereas, the bromo group were found to be unable to induce the activity. The presence of electron-withdrawing groups such as the chloro group at 7th position enhanced the COX-2 selectivity in comparison to electron-donating groups (**Figure 3**).

4.3. Essential fatty acids

Essential fatty acids are long-chain fatty acid compounds containing methyl and carboxylic acids at both terminal ends. The degree of saturation and length of hydrocarbon chain varies and plays an important role in physical properties. Long-chain polyunsaturated fatty acid (PUFA) helps in reducing the secretion of proinflammatory factors as well as reduces MMP production [92]. The fatty acids exhibiting therapeutic activity in the management of OA [93-95] are given in **Table 2** .

4.4. Essential oils

Essential oils (EO) are volatile, aromatic, lipophilic liquids having a characteristic odour and can be obtained from almost any part of the plant, i.e., flowers, leaves, rhizomes, seeds, peels, barks, etc. EOs are mixtures of 60-300 non polar and semi-hydrophilic components of low molecular weight at varying concentrations. EOs are majorly made up of terpenes & terpenoids, straight-chain compounds, aromatic and phenolic compounds in addition to sulphur derivatives. Among these, terpenoids and phenolic compounds constitute for a large portion of EOs. In essence, terpenes are secondary metabolic product containing an isoprene (2-methylbuta-1,3-diene) backbone and reactions such as oxidation and rearrangement caused by the biochemical process leads to the development of terpenoids [96].

Aromatic and phenolic compounds present in EOs exhibit an array of therapeutic activities and can be used for the treatment of multiple ailments or conditions ranging from headache to cancer. In the case of OA, phenolic components can interact with a number of enzymes or receptors involved in the degeneration cascade of cartilage, such as reduction of pain & inflammation by inhibiting COX enzymes [97–106], inhibition of MMPs [107–111] along with modulation of cytokines as well as pro-inflammatory factor [112–117] are stated in **Table 2, Table 3** and **Table 4,** respectively. To exhibit maximum inhibition of COX enzymes, the phenolic component should have a sterically free phenolic hydroxyl group (**Figure 3**). On the other hand, COX inhibiting potency of phenolic compounds can be escalated by substitution with electron-donating or hydrophobic groups [105].

4.5. Flavonoids

Flavonoids are one of the most commonly used phytochemicals exhibiting multiple activities and are present in various vegetables and fruits. Chemically, flavonoids are 15 carbon molecules containing two benzene rings joined together via a pyran ring. The flavonoids can be further categorised into subclasses depending upon structural modifications such as flavones, flavonols, flavanones, flavanonols, flavanols, isoflavones, neoflavonoids, anthocyanidins and chalcones. The use of flavonoids is well explored in the management of OA since it inhibits cyclooxygenase enzymes [118–120], modulates MMPs [121–132] as well as NF-κB dependent pro-inflammatory cytokines [133–151] to exhibit analgesic, anti-inflammatory and antioxidant properties. In contrast to synthetic molecules, flavonoids such as apigenin (**Table 2, Table 3** and **Table 4**) are reported to be a safe natural compound and act on several possible targets to provide relief in knee OA [152]. The interaction of flavonoids with multiple receptors depends upon various parameters such as the number of hydroxyl groups present and their location as well as the presence of other groups. The SAR for flavonoids has been well documented in the literatures [153]. B ring containing the dihydroxy groups (ortho to each other) stabilizes the phenoxy radical after deprotonation by participating in resonance or electron delocalization. On the other hand, C ring can further help in the stabilization of phenoxyl radical from B ring if C ring contains a 2,3-double bond coupled with 4-oxo group. Hydroxy group present at 5th and 7th position of A ring and 4th position of B ring

plays an important role in the activity demonstration. Presence of hydroxy groups at 3th and 5th position can moderate the activity of flavonoids. Glycosylation of the hydroxyl group present at the 7th position escalates the flavonoid solubility while reducing the anti-inflammatory activity. Replacement of the hydroxyl group with then methoxy group at 7th position moderates the intensity of action. In addition, the presence of a double bond at C_2-C_3 position of C ring plays an important role in Nrf_2 activation (**Figure 3**), which alarms the body regarding oxidative damage and triggers the body's defense mechanism by activating the production of protective antioxidant moieties.

4.6. Glycosides

Glycosides can be defined as condensation products of carbohydrates with a range of organic hydroxy (infrequently thiol) compounds present as monohydrates to promote the participation of the hemiacetal part of the sugar molecule in the condensation reaction. In simple words, glycosides are composed of a sugar moiety called glycone part joined together with non-carbohydrate fragments known as aglycones via a glycosidic linkage [154].

Glycosides can be differentiated as O-glycoside, S-glycoside, N-glycoside, and C-glycoside depending upon the presence of the group at the linkage. However, the most acceptable classification of a glycoside is based upon the nature of aglycone moieties such as anthracene glycosides, cyanogenetic glycosides, saponin glycosides, etc. Glycoside displays multiple therapeutic activities such as cardiotonic, analgesic, anti-rheumatic. Glycosides exhibit therapeutic activity in OA by inhibiting the production of proinflammatory factors and cytokines [155–157] to retard cartilage degradation are presented in **Table 4**.

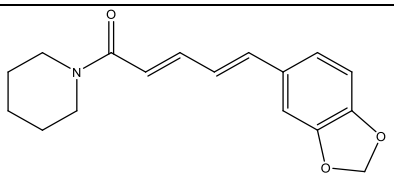
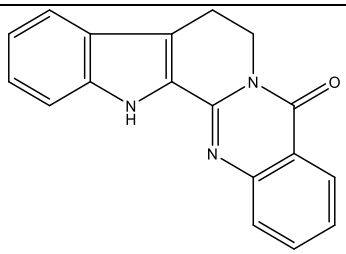
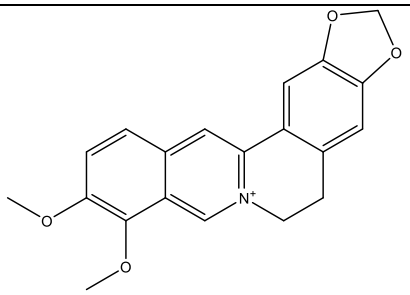
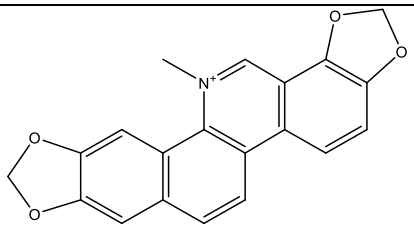
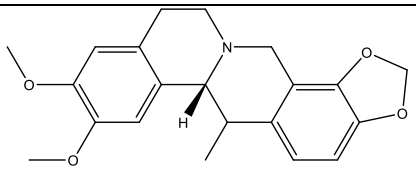
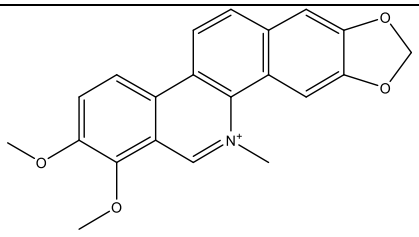
4.7. Lignans

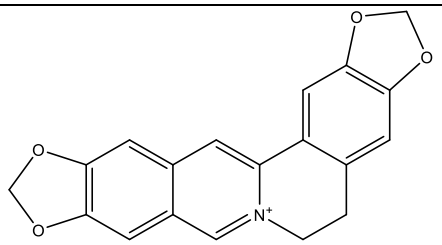
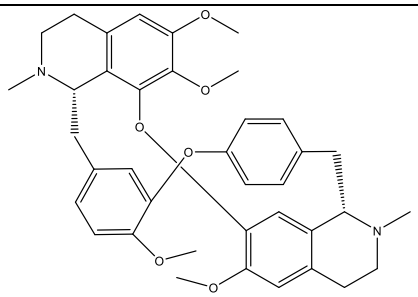
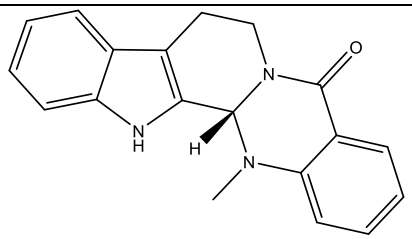
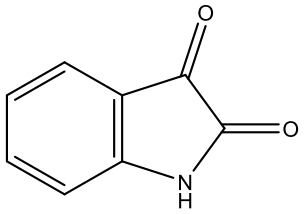
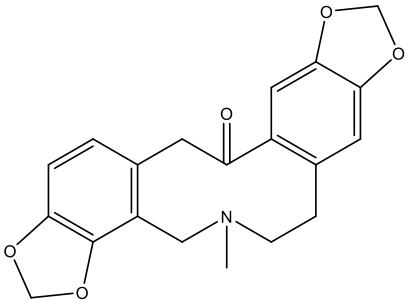
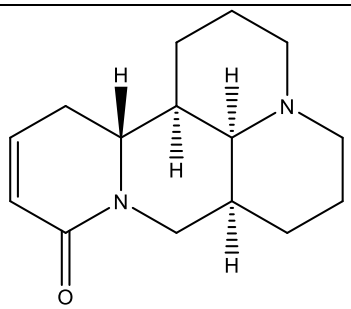
Lignans are low molecular weight metabolic products formed due to oxidative coupling of *p*-hydroxyphenylpropene units joined together via oxygen linkage. The lignans formed via coupling of acids and/or alcohol are called Haworth lignans while lignans formed due to pairing of propenyl and/or allyl derivatives are called neolignans [158]. Generally, lignans are synthesized by the reduction of ferulic acid into coniferyl alcohol followed by oxidative dimerization to establish a linkage via β-carbon of C_3 side chain (**Figure 3**). They are most commonly acquired from roots, fruits, heartwoods, as well as resinous plant exudates. Lignans exhibiting therapeutic activity against OA by modulating the release of proinflammatory factors [159–164] and proliferation of MMP enzymes [165–170] are presented in **Tables 3** and **Table 4,** respectively.

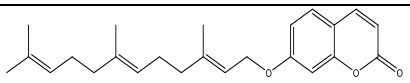
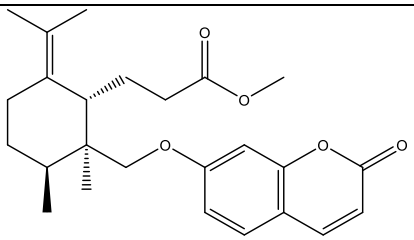
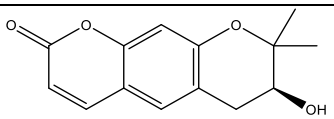
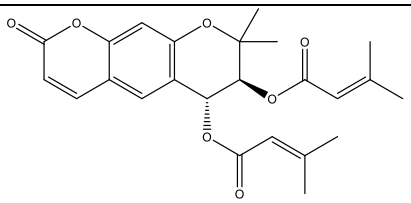
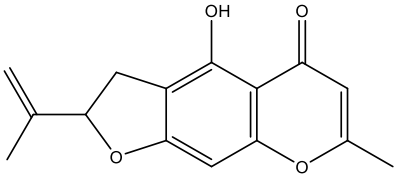
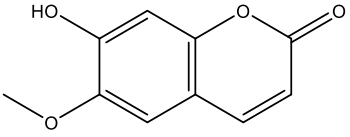
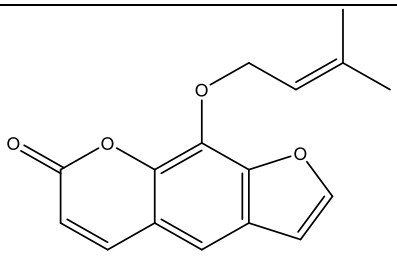
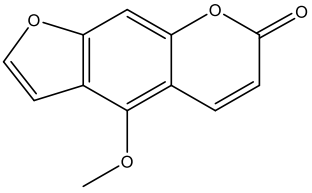
4.8. Pentacyclic and Steroidal triterpenoids

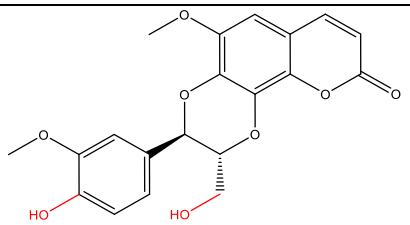
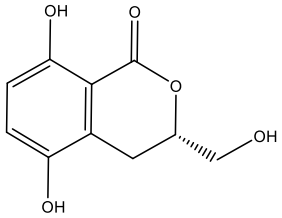
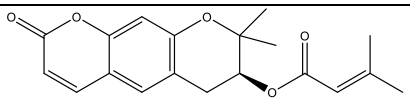
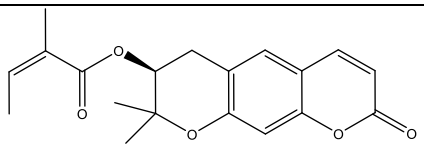
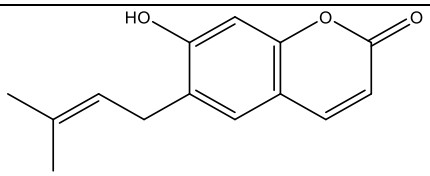
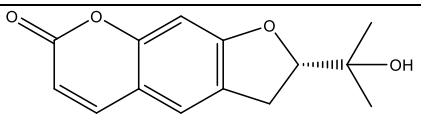
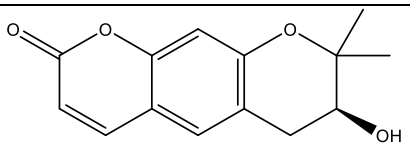
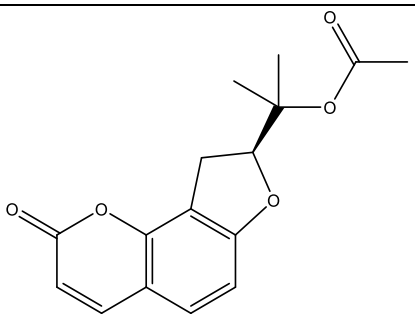
Triterpenoids are metabolic products containing 6 isoprene units and shares structural similarity with squalene. Depending upon the modes involved in the ring closure, triterpenoids with different skeleton structures will be produced. Currently, more than 4000 naturally produced triterpenoids are known with 40 different skeleton structures. Triterpenoids with 27-carbon atoms are known as steroidal triterpenoids, whereas 30-carbon structures are called pentacyclic triterpenoids [171]. Steroidal triterpenoids (**Figure 3**) inhibiting the proliferation of COX [86,172,173] and MMPs [174–177] are stated in **Table 2** and **Table 3,** respectively, whereas pentacyclic triterpenoids modulating the release of proinflammatory factors [178,179] are represented in **Table 4**.

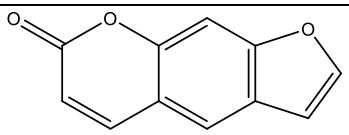
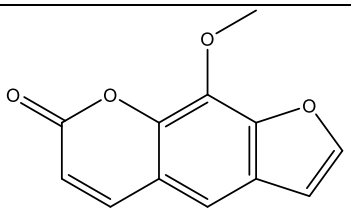
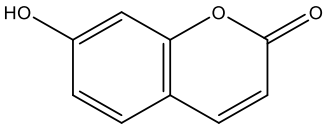
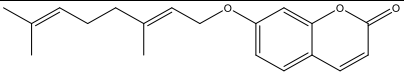
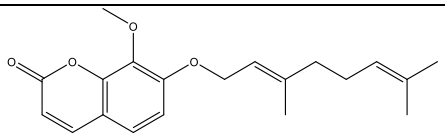
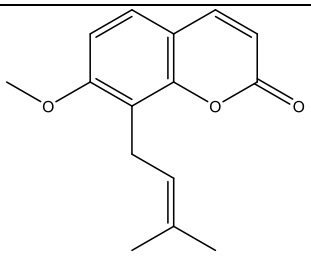
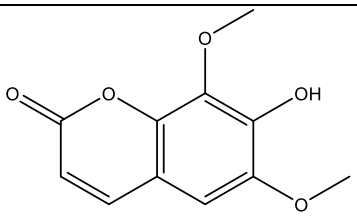
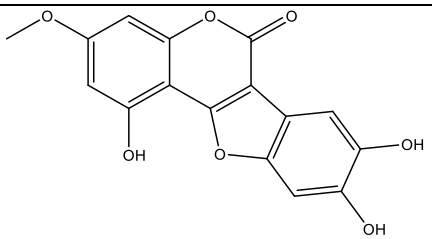
Table 2: Phytomolecules exhibiting cyclooxygenase inhibitory activity

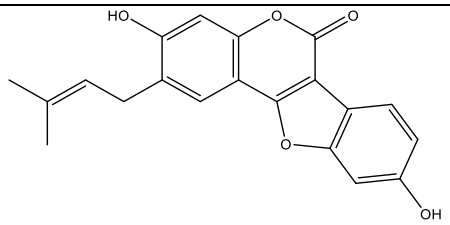
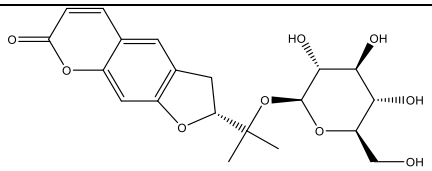
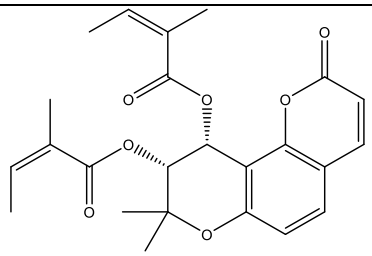
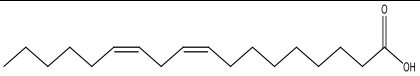
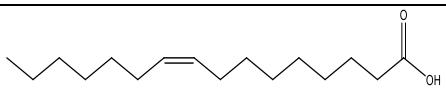
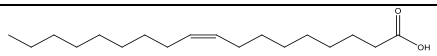
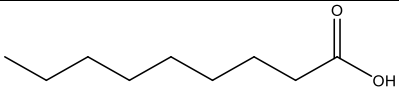
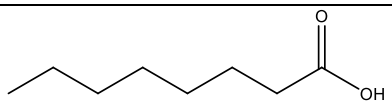
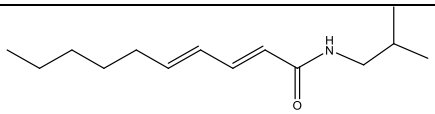
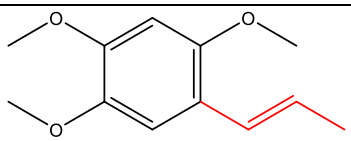
Compounds	Biological sources	Selectivity	Chemical structure
Alkaloids			
Piperine	Piper nigrum	COX-2	
Rutaecarpine	Evodia rutaecarpa	Both	
Berberine	Berberis vulgaris	COX-2	
Sanguinarine	Sanguinaria canadensis	Both	
Cavidine	Corydalis impatiens	COX-2	
Chelerythrine	Chelidonium majus	COX-2	

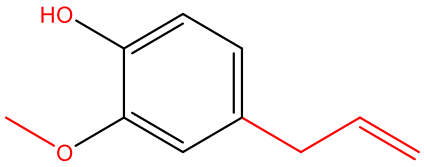
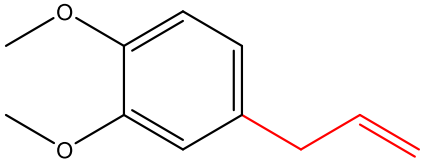
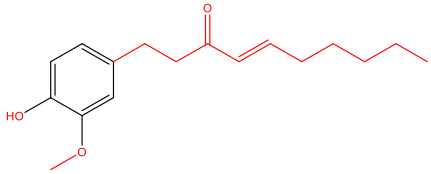
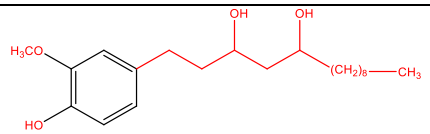
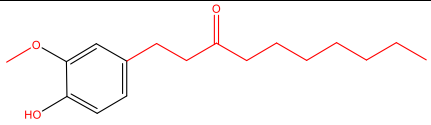
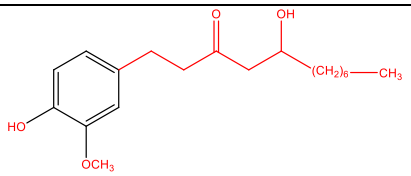
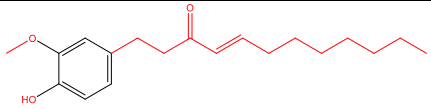
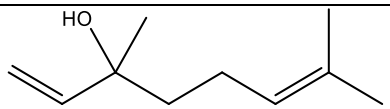
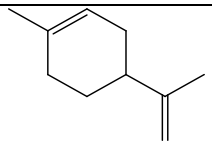
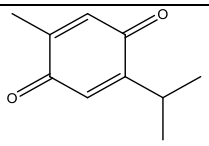
Pseudocoptisine	Corydalis turtschaninovi	COX-2	
Tetrandrine	Stephania tetrandra	Both	
Evodiamine	Evodia rutaecarpa	COX-2	
Isatin	Couroupita guianensis	COX-2	
Protopine	Papaver somniferum	COX-2	
Sophocarpine	Sophora alopecuroides	COX-2	

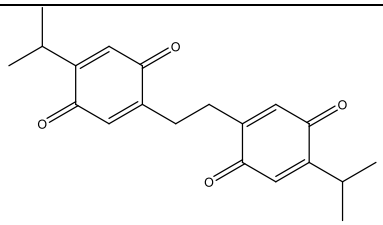
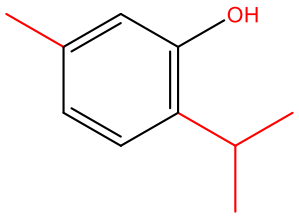
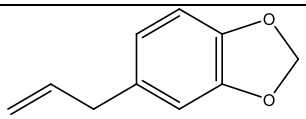
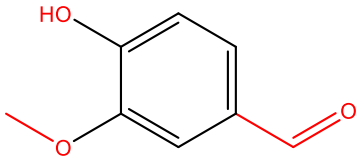
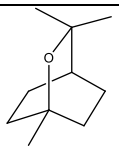
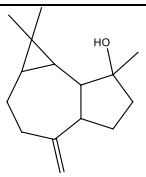
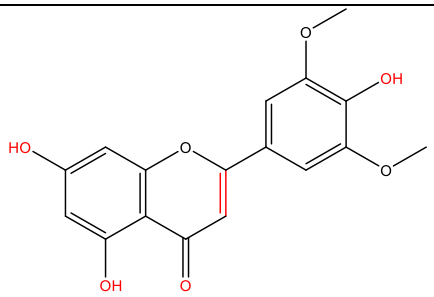
Coumarins			
Umbelliprenin	Ferula szowitsiana	COX-2	
Methyl galbanate	Ferula szowitsiana	COX-2	
Edulisin II	Angelica decursiva	COX-2	
Decursidin	Angelica decursiva	COX-2	
Heterocarpin	Corydalis heterocarpa	COX-2	
Scopoletin	Foeniculum vulgare	-	
Imperatorin	Foeniculum vulgare	-	
Bergapten	Euodia daniellii	COX-2	

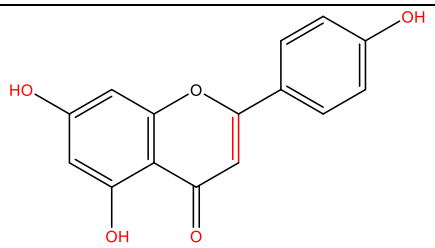
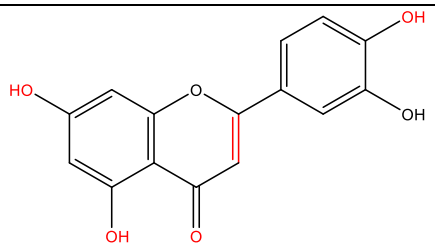
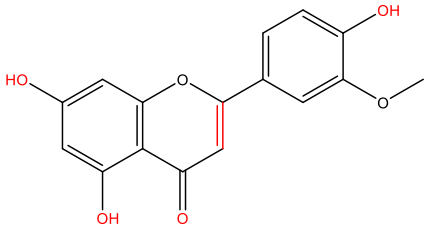
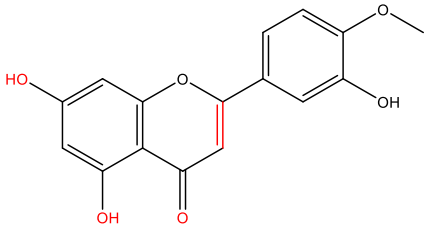
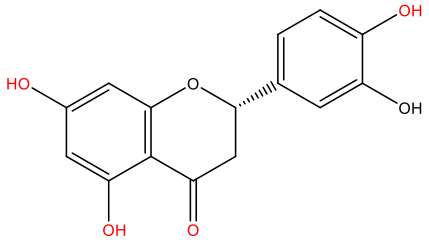
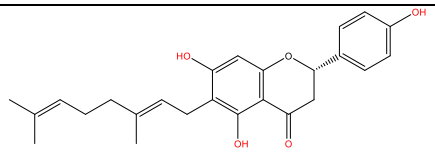
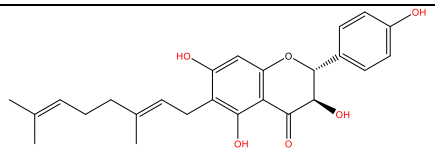
Cleomiscosins	Cleome viscosa	COX-2	
Botryoisocoumarin A	Kandelia candel	COX-2	
Decursin	Angelica gigas	COX-2	
Decursinol angelate	Angelica gigas	COX-2	
7-demethylsuberosine	Angelica gigas	COX-2	
Marmesin	Angelica gigas	COX-2	
Decursinol	Angelica gigas	COX-2	
Libanoridin	Corydalis heterocarpa	COX-2	

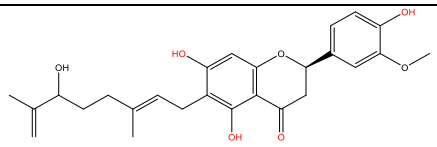
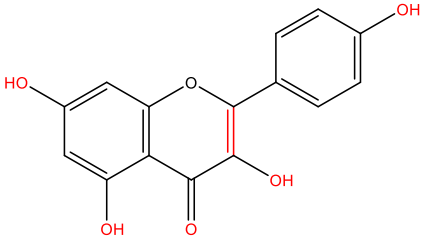
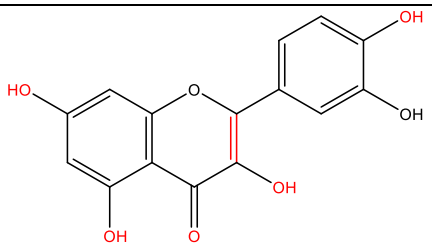
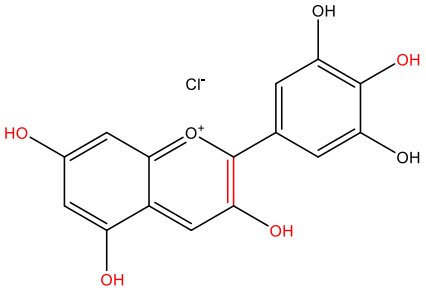
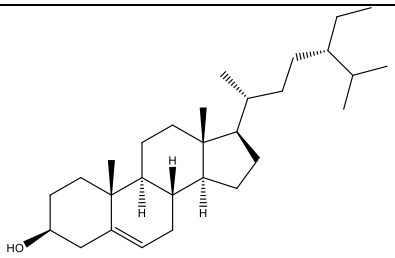
Psoralen	Dystaenia takeshimana	COX-2	
Xanthotoxin	Dystaenia takeshimana	COX-2	
Umbelliferone	Dystaenia takeshimana	COX-2	
Auraptene	Poncirus trifoliate	COX-2	
Collinin	Zanthoxylum schinifolium	COX-2	
Osthole	Cnidium monnieri	COX-2	
Isofraxidin	Artemisia persica	COX-2	
Wedelolactone	Wedelia chinensis	COX-2	

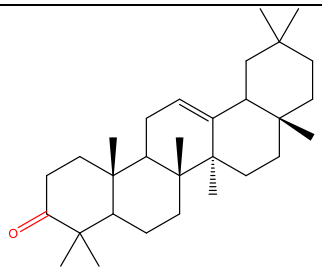
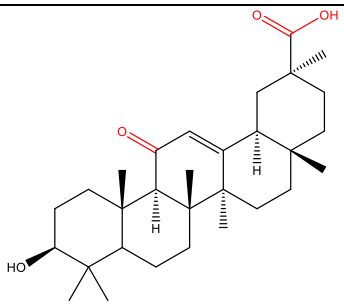
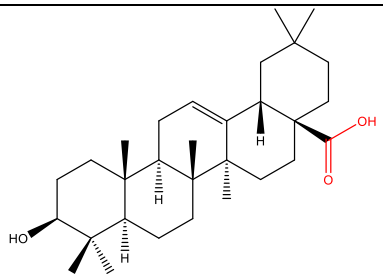
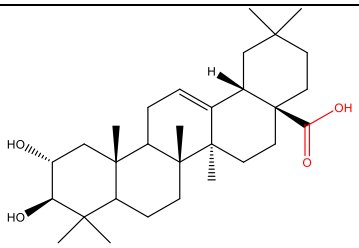
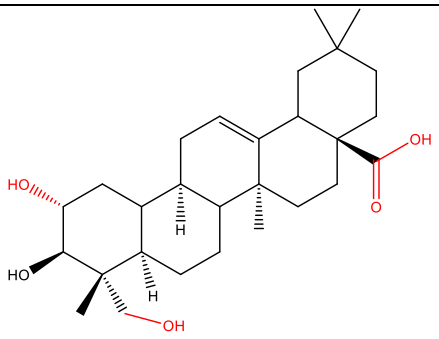
Psoralidin	Psoralea corylifolia	COX-2	
Nodakenin	Angelica gigas	COX-2	
Anomalin	Saposhnikovia divaricata	COX-2	
Essential fatty acids			
Linoleic acid	Juglans regia	Both	
Palmitoleic acid	Macadamia integrifolia	COX-1	
Oleic acid	Cynodon dactylon	COX-1	
Nonanoic acid	Piper nigrum	COX-1	
Octanoic acid	Piper nigrum	COX-1	
Pellitorine	Piper sarmentosum	COX-1	
Essential oils			
α-Asarone	Daucus carota	Both	

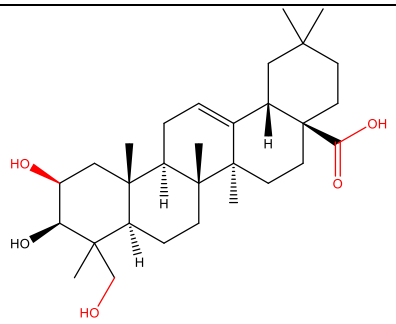
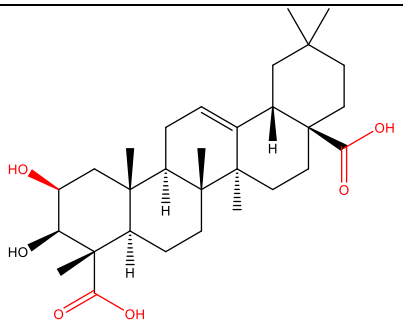
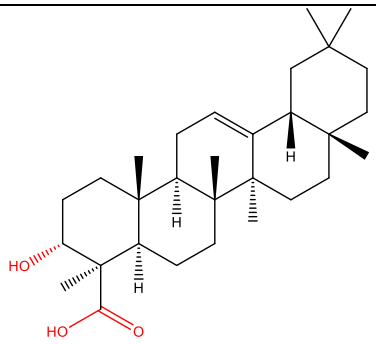
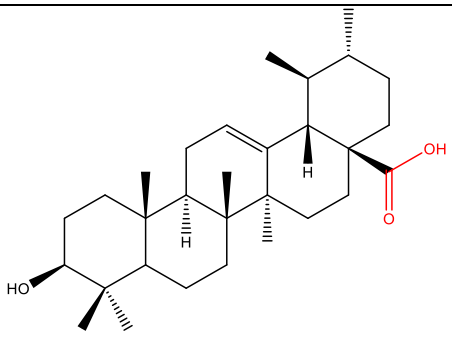
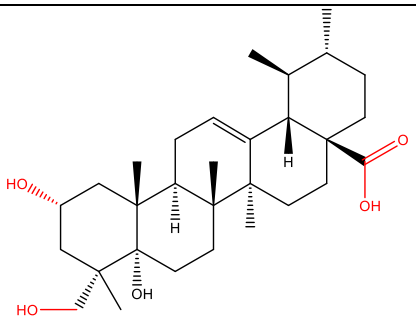
Eugenol	Piper nigrum	COX-2	
Methyl eugenol	Piper nigrum	Both	
6-Shogaol	Zingiber officinale	COX-2	
8-Gingerdiol	Zingiber officinale	COX-2	
6-Paradol	Zingiber officinale	COX-2	
8-Gingerol	Zingiber officinale	COX-2	
8-Shogaol	Zingiber officinale	COX-2	
Linalool	Acorus calamus	COX-2	
Limonene	Carum carvi	COX-1	
Thymoquinone	Nigella sativa	Both	

Dithymoquinone	Nigella sativa	Both	
Thymol	Nigella sativa	Both	
Nonanal	Piper nigrum	-	
Safrole	Piper nigrum	COX-1	
Vanillin	Zingiber cassumunar	COX-2	
1,8-Cineol	Zingiber officinale	COX-1	
Spathulenol	Hymneae courbaril	COX-2	
Flavonoids			
Chrysin	Oroxylum indicum	COX-1	

Apigenin	Apium graveolens	COX-2	
Luteolin	Colchicum luteum	Both	
Chrysoeriol	Artemisia absinthium	COX-2	
Diosmetin	Dracocephalum heterophyllum	COX-2	
Eriodictoyl	Eriodictyon californicum	COX-2	
Bonannione A	Schizolaena hystrix	Both	
Bonnaniol	Schizolaena hystrix	COX-2	

Tomentodiplacone	Paulownia tomentosa	COX-1	
Kaempferol	Spinacia oleracea	Both	
Quercetin	Vaccinium oxycoccos	COX-2	
Delphinidin	Vaccinium angustifolium	COX-2	
Pentacyclic and steroidal triterpenoids			
β-Sitosterol	Zingiber officinale	COX-2	

β-Amyrone	Protium paniculatum	COX-1	
Glycyrrhetinic acid	Glycyrrhiza glabra	Both	
Oleanolic acid	Olea europaea	Both	
Maslinic acid	Salvia canariensis	Both	
Arjunolic acid	Terminalia arjuna	Both	

Bayogenin	Medicago truncatula	COX-2	
Medicagenic acid	Medicago truncatula	Cox-2	
α-Boswellic acid	Boswellia serrata	Both	
Ursolic acid	Salvia rosmarinus	Both	
Asiatic acid	Centella asiatica	Both	

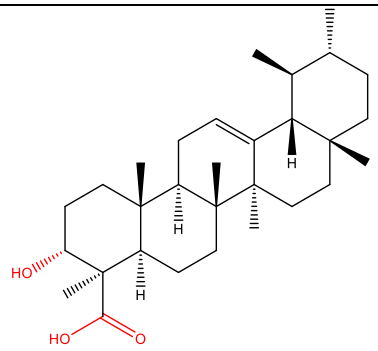
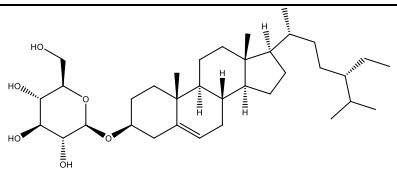
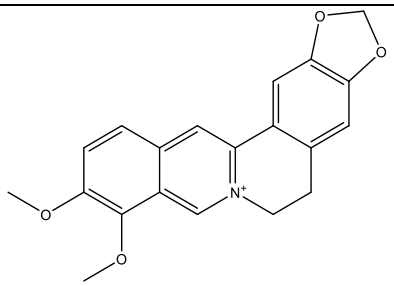
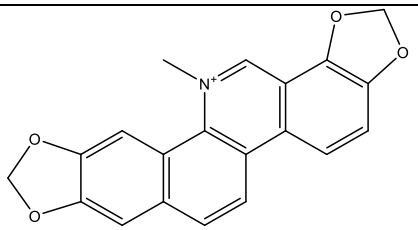
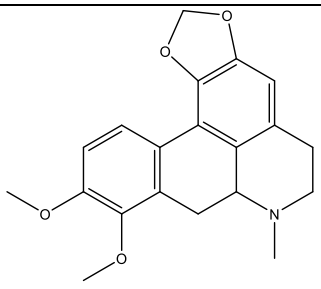
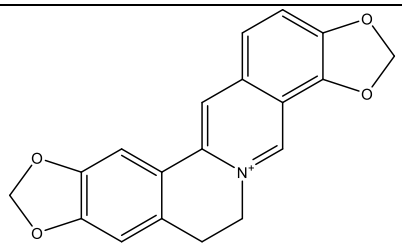
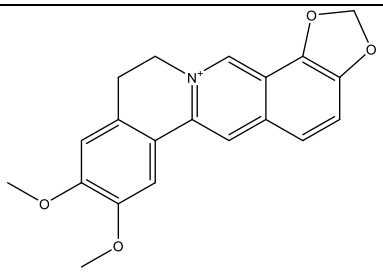
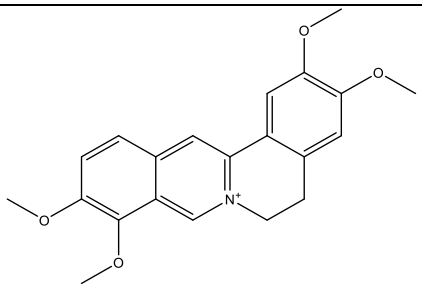
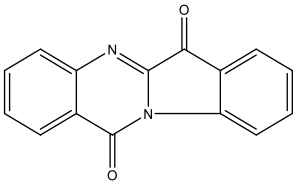
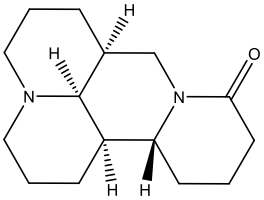
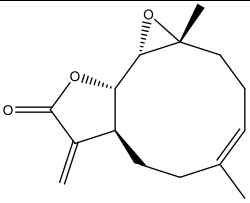
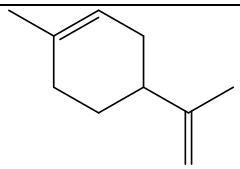
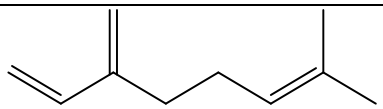
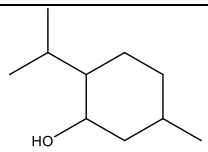
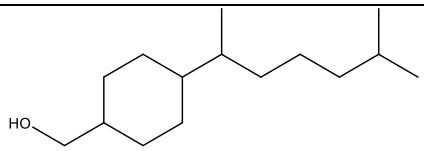
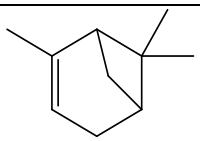
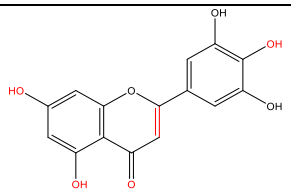
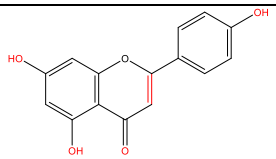
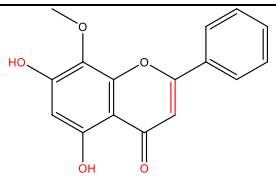
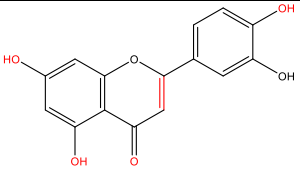
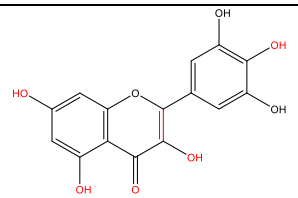
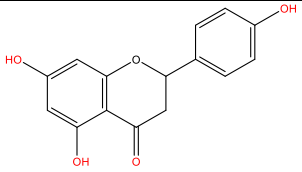
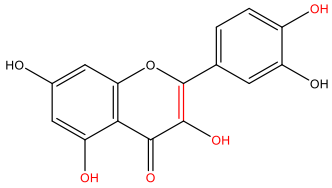
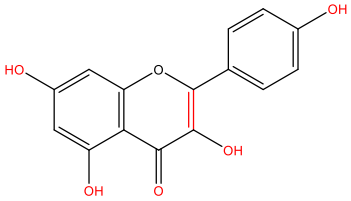
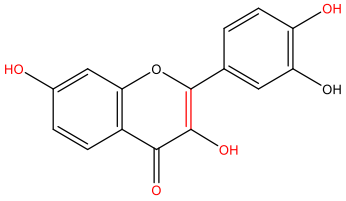
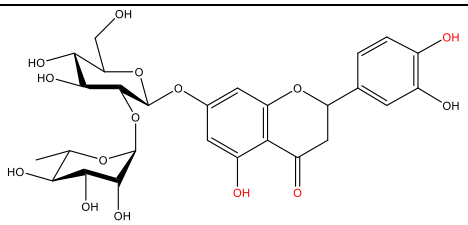
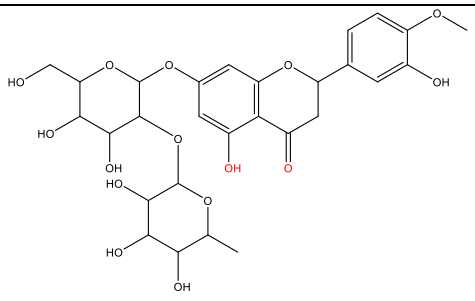
β-Boswellic acid	Boswellia serrata	Both	
Daucosterol	Dystaenia takeshimana	COX-2	

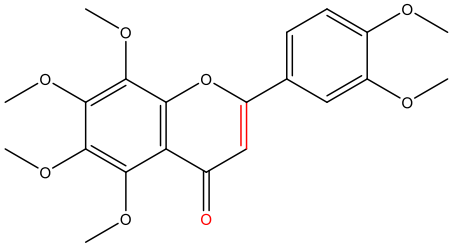
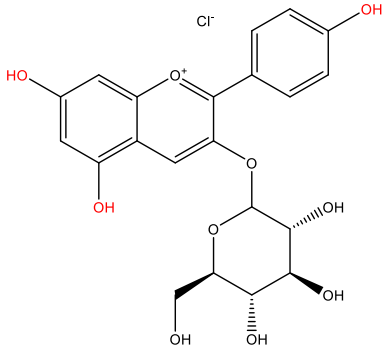
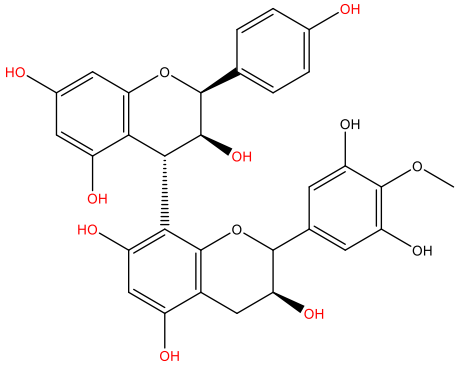
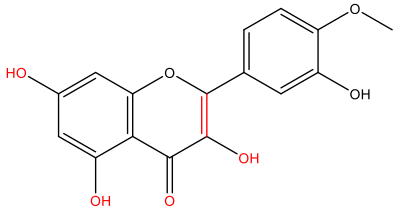
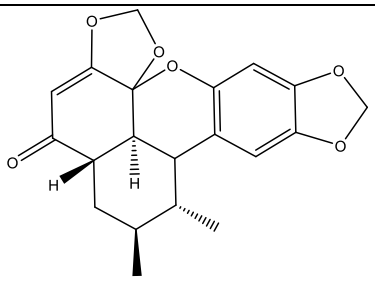
Table 3: Potential phytochemicals exhibiting prominent inhibitory activity against matrix metalloproteinase (MMPs)

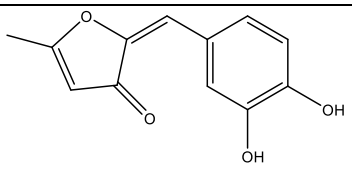
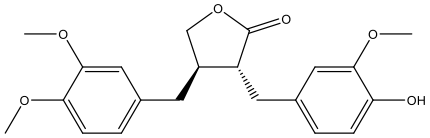
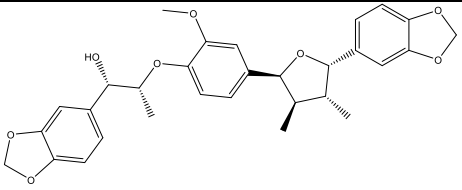
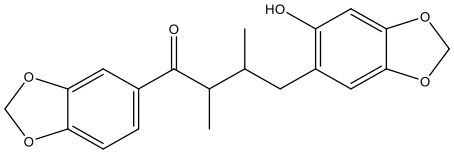
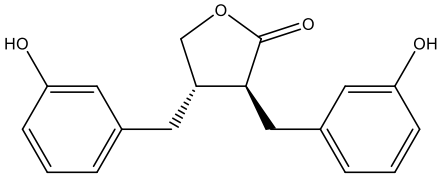
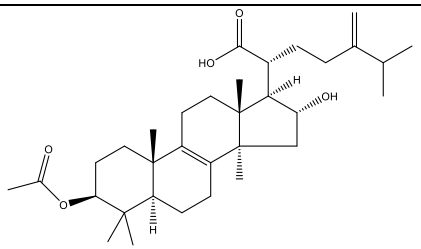
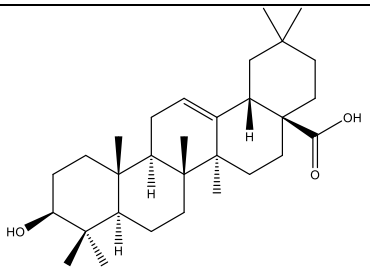
Compounds	**Biological sources**	**Chemical structure**
Alkaloids		
Berberine	Berberis heterophylla	
Sanguinarine	Sanguinaria canadensis	
Crebanine	Stephania hainanensis	

Coptisine	Coptis japonica	
Epiberberine	Berberis aristata	
Palmatine	Phellodendron amurense	
Tryptanthrin	Isatis indigotica	
Matrine	Radix sophorae	
Essential oils		
Parthenolide	Tanacetum parthenium	

Limonene	Carum carvi	
Myrcene	Cymbopogon citratus	
Menthol	Mentha piperita	
Bisabolol	Teucruim alopecurus	
α-Pinene	Rosmarinus officinalis	
Flavonoids		
Tricetin	Eucalyptus globulus	
Apigenin	Chamomilla recutita	
Wogonin	Scutellaria baicalensis	
Luteolin	Colchicum luteum	

Myricetin	Myristica fragrans	
Naringenin	Citrus paradisi	
Quercetin	Vaccinium oxycoccos	
Kaempferol	Spinacia oleracea	
Fisetin	Rhus cotinus	
Neoeriocitrin	Allium cepa	
Neohespiridin	Citrus sinensis	

Nobiletin	Citrus sinensis	
Anthocyanin	Rubus occidentalis	
Proanthocyanidin	Triticale straw	
Tamarixentin	Azadirachta indica	
Lignans		
Sauchinone	Saururus chinensis	

Inotilone	Inonotus linteus	
Arctigenin	Arctium lappa	
Saucerneol F	Saururus cernuus	
Saucerneol G	Saururus cernuus	
Enterolactone	Linum usitatissimum	
Pentacyclic and steroidal triterpenoids		
Pachymic acid	Poria cocos	
Oleanolic acid	Olea europaea	

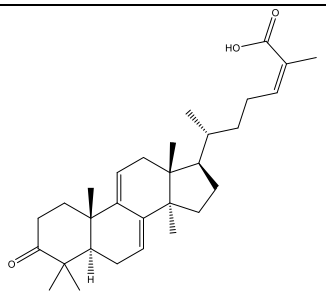
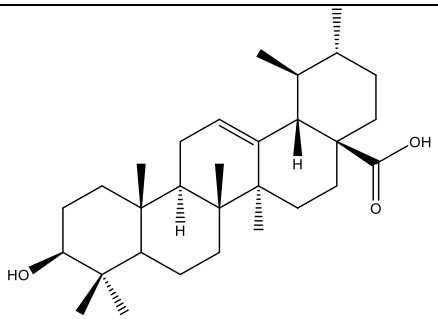
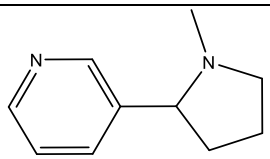
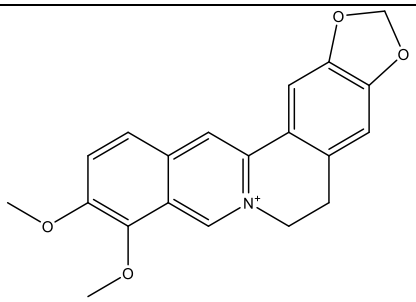
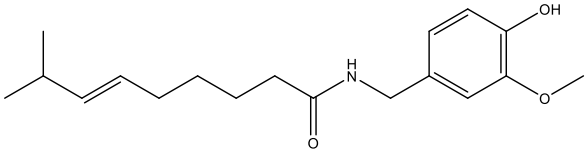
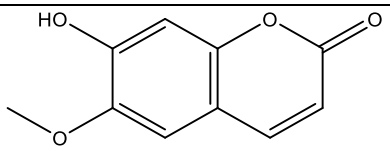
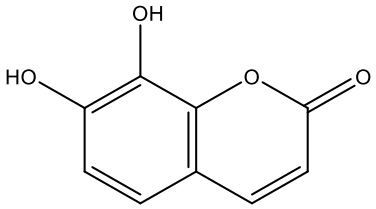
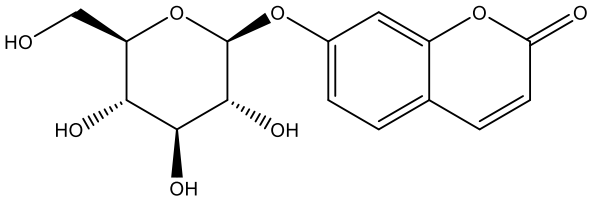
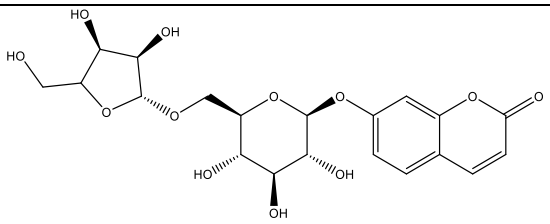
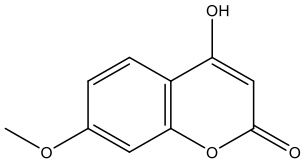
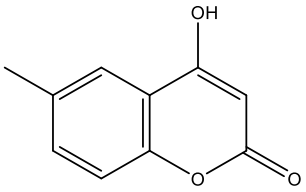
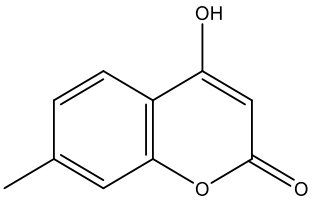
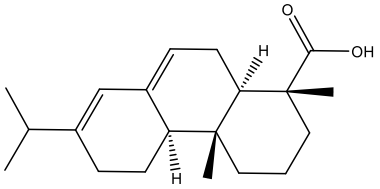
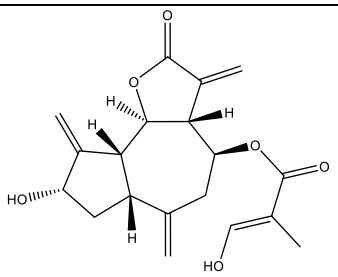
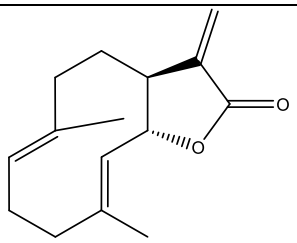
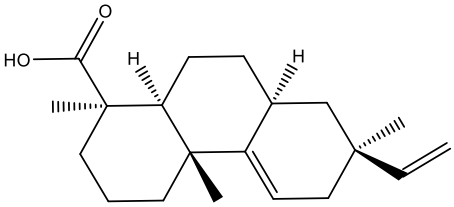
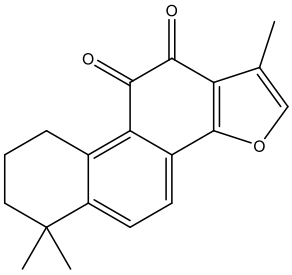
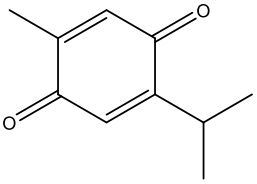
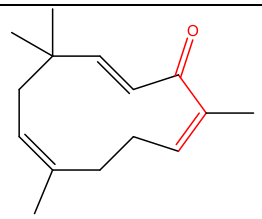
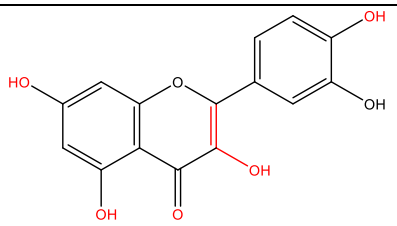
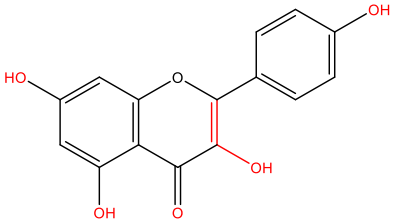
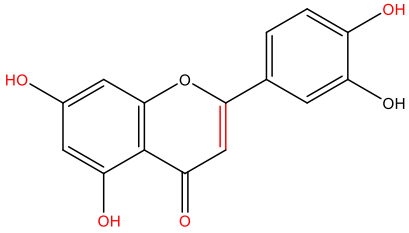
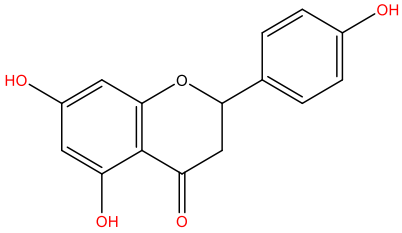
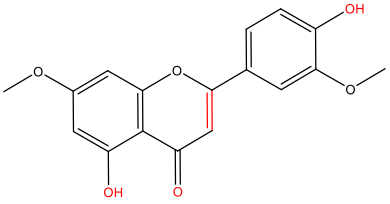
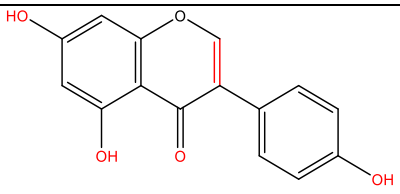
Ganoderic acid	Ganoderma lucidum	
Ursolic acid	Salvia rosmarinus	

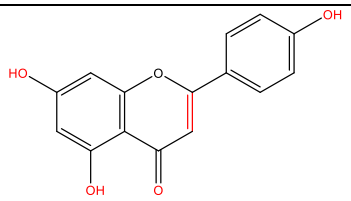
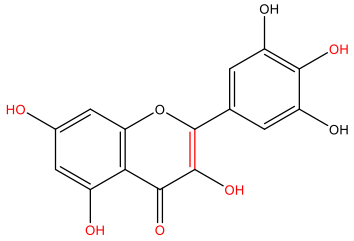
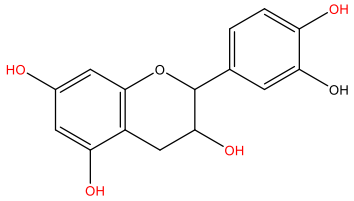
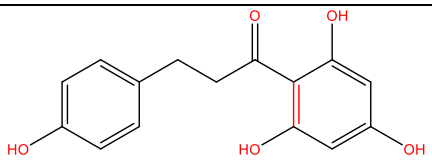
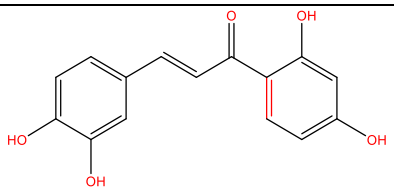
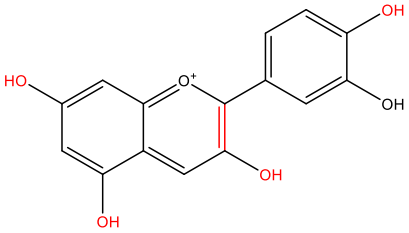
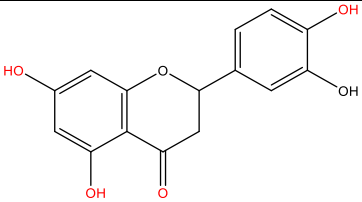
Table 4: Phytochemicals demonstrating cytokine modulatory effects

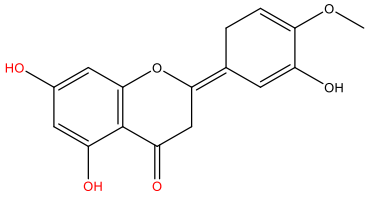
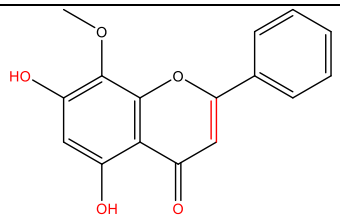
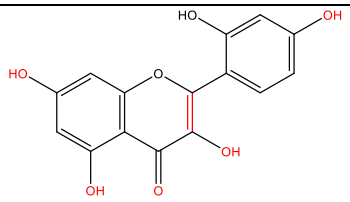
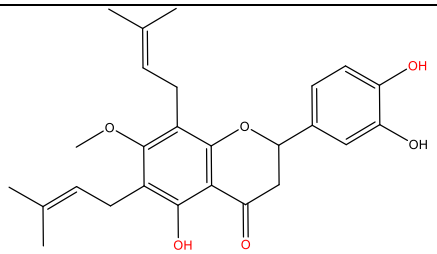
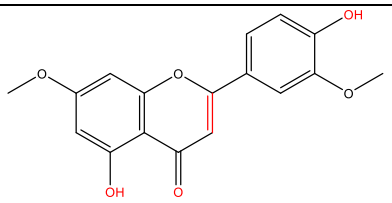
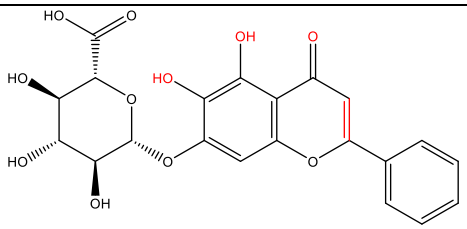
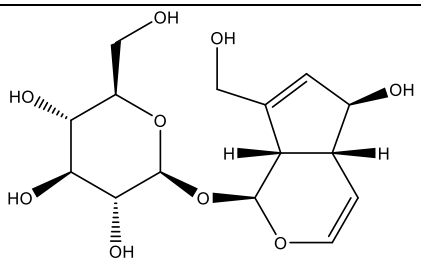
Compounds	**Biological sources**	**Chemical structure**
Alkaloids		
Nicotine	Nicotiana tabacum	
Berberine	Berberis heterophylla	
Capsaicin	Capsicum annum	
Coumarins		

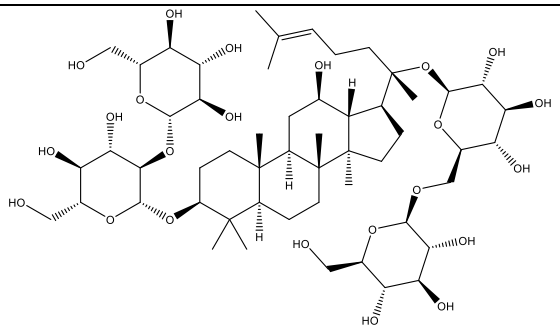
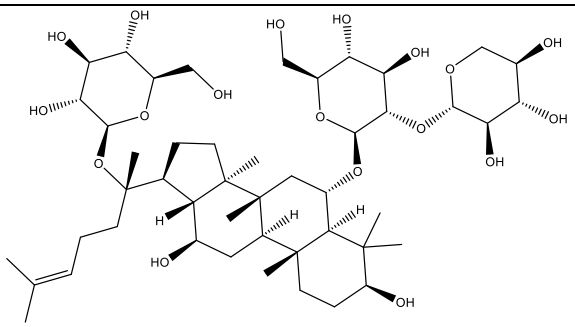
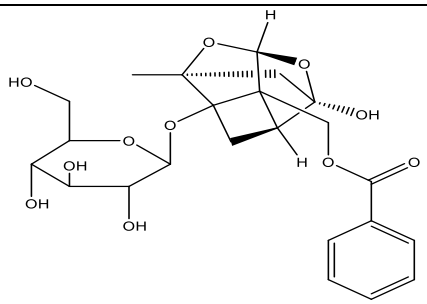
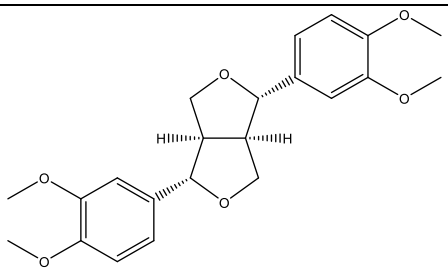
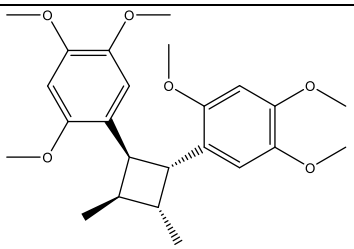
Scopoletin	Scopolia carniolica	
Daphnetin	Daphne kamtschatica Maxim	
Skimmin	Hydrangea paniculate	
Apiosylskimmin	Hydrangea paniculate	
4-Hydroxy-7-methoxycoumarin	Angelica accutiloba	
4-Hydroxy-6-methylcoumarin	Angelica accutiloba	
4-Hydroxy-7-methylcoumarin	Angelica accutiloba	
Essential oils		

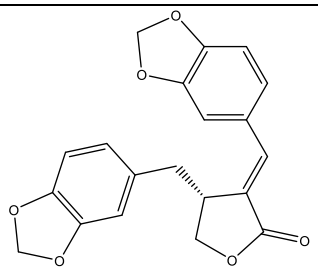
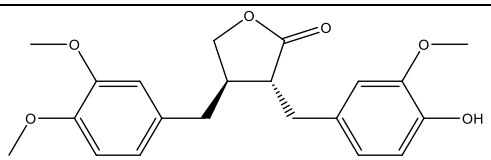
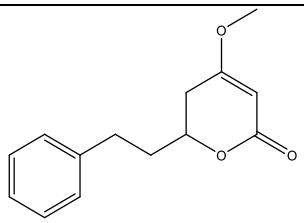
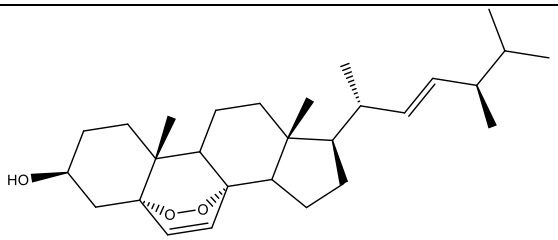
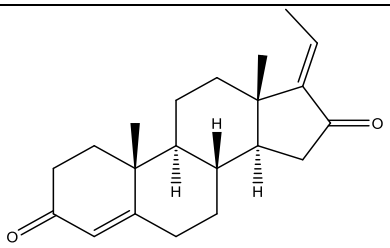
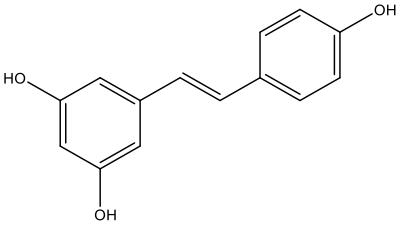
Abietic acid	Abies grandis	
Cynaropicrin	Saussurea lappa	
Costunolide	Saussurea lappa	
Acanthoic acid	Acanthopanax koreanum	
Tanshinone IIA	Salvia Miltiorrhiza	
Thymoquinone	Nigella sativa	
Flavonoids		

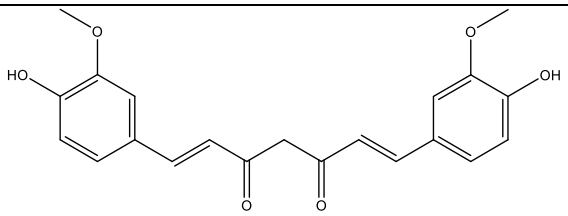
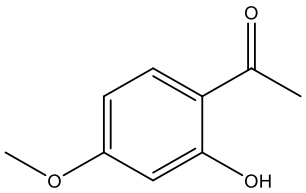
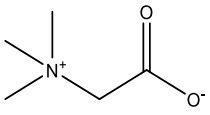
Zerumbone	Zingiber zerumbet	
Quercetin	Brassica oleracea	
Kaempferol	Capsicum annum	
Luteolin	Perilla frutescens	
Naringenin	Citrus paradisi	
Velutin	Euterpe oleracea	
Genistein	Glycine max	

Apigenin	Apium graveolens	
Myricetin	Brassica oleracea	
Catechin	Camellia sinensis	
Phloretin	Malus domestica	
Butein	Dalbergia odorifera	
Cyanidin	Prunus cerasus	
Eriodictyol	Thymus vulgaris	

Hesperetin	Citrus sinensis	
Wogonin	Scutellaria baicalensis	
Morin	Psidium guajava	
Amoradicin	Amorpha fruticosa	
Velutin	Euterpe oleracea	
Baicalin	Scutellaria galericulata	
Glycosides		
Aucubin	Auciba japonica	

Ginsenoside Rb1	Panax notoginseng	
Notoginsenoside R1	Panax notoginseng	
Paeoniflorin	Moutan cortex	
Lignans		
Eudesmin	Magnolia fargesii	
Magnosalin	Perilla frutescens	

Savinin	Pterocarpus santalinus	
Arctigenin	Arctium lappa	
Dihydrokavain	Piper methysticum	
Pentacyclic and steroidal triterpenoids		
Ergosterol peroxide	Sarcodon Aspratus	
Guggulsterone	Commiphora mukul	
Miscellaneous		
Resveratrol	Vitis vinifera	

Curcumin	Curcuma longa	
Paeonol	Paeonia suffruticosa	
Betaine	Spinacia oleracea	

5. CHALLENGES IN THE DEVELOPMENT OF PHYTOCHEMICAL LOADED TOPICAL FORMULATIONS

Literatures implies that the regular intake of dietary phytochemicals helps in the management of various ailments, mainly in chronic disorders. However, their application for the treatment is very limited due to various factors such as their unavailability in the market, adulteration, hindered bioavailability, poor aqueous solubility, poor stability and deprived pharmacokinetic profile. The scale-up of oral and parenteral phytopharmaceuticals exhibit multiple limitations such as complex product development process, and high end equipments, which ultimately leads to high price, patient non-compliance, etc.

On the other hand, scale-up of topical delivery systems are easy as well as cheaper than the oral or parenteral delivery systems. Besides, topical preparations bypass first-pass metabolism, eliminate the chances of severe side effects and reduce the dose-dosage regimen while enhancing patient compliance due to its easy application. However, there are multiple factors related to phytochemicals which limit their incorporation in topical phytopharmaceuticals [180].

5.1. Partition coefficient

According to Meyer–Overton theory of absorption, lipophilic compounds can rapidly cross the cell membrane because of their lipid nature, while hydrophilic compound shows a slower absorption rate as it involves hydration of cell wall proteins. The partition coefficient can be defined as the property of the molecule to partition between two non-miscible phases. In other words, the partition coefficient is the ratio of amount of drug present in organic phase to an aqueous phase. Experimentally, the hydrophobicity of the compound can be calculated by determining its relative distribution in an *n*-octanol/water mixture. Hydrophobic molecules prefer to stay in the organic phase due to which they have a higher *P*-value and can easily cross the stratum corneum. To secure absorption through topical application, the phytomolecule should get partitioned in the stratum corneum, which is the rate-limiting step in permeation [181].

Compounds having log *P* values in between 1-3 gets absorbed through intercellular lipid and aqueous pathways, whereas substances with log *P* of more than 3 mainly permeate through the intercellular lipid pathway. Therefore, compounds having balanced aqueous organic solubility are ideal for topical preparation [182]. However, most of the phytochemicals displaying reliable activity against OA are lipophilic in nature.

4.2. Molecular size and shape:

The molecular volume and shape of a compound play an important role in its permeation through topical administration. The shape of a molecule is assumed as spherical, whereas instead of molecular volume, molecular weight is considered due to suitability and practicality reasons. Compounds with smaller molecular weight exhibit rapid diffusion in comparison with high molecular weight. Various studies suggest the molecular weight of 500 Da as a ceiling point, above which the rate of diffusion decreases and results in lower absorption [183]. Functionalization of steroidal compounds with polar functional groups leads to reduction in permeability through the stratum corneum than their parent compounds [184].

5.3. Solubility/ melting point

The percutaneous permeation can be significantly influenced by the solubility of a chemical entity and its partition co-efficient. In general, the permeation of lipophilic compounds through the stratum corneum is more rapid than water-soluble compounds. However, the solubility of chemical substances should be efficiently balanced to exhibit better permeability in the lipophilic stratum corneum as well as hydrophilic viable epidermis and dermis layers. Apart from solubility, the partitioning of drug molecules among the stratum corneum and vehicle plays a crucial character in the permeation process. Complete solubilisation of molecules in the continuous phase exhibits enhanced penetration owing to the higher flux gradient across the vehicle/skin interface. For example, water-insoluble steroidal substances show partial solubility in FDA approved vehicles due to which they are easily partitioned into the stratum corneum causing depletion in a vehicle followed by a reduction in flux gradient essential for diffusion [185].

5.4. Ionization

Degree of ionization and its impact on solubility plays an important role in the permeation of drugs into the skin. According to pH partition theory, the unionized molecule exhibits a higher permeability coefficient in comparison with the ionized molecule through the stratum corneum via lipophilic intercellular pathways. Thus, the free acidic or alkali molecules are best suited for topical formulation. However, the equation given by Hadgraft and Valenta states that the total flux (J_{total}) of a drug molecule through the skin combines both ionized as well as unionized species [187].

$$J_{total} = k_P^{union} . C_{union} + k_P^{ion} . C_{ion}$$

Unionized molecules display higher permeability and lower solubility compared to ionized species. However, the higher solubility of ionized species can compensate for their lower permeability, and thus the flux developed from each species can be comparable. Therefore, the influence of pH on permeability should be explored so as to maximize the total flux created by combining unionized as well as ionized species. For example, the calculated

skin permeation (Log Kp) for lidocaine (topical anaesthetic) was found to be -6.12cm/s whereas ionized lidocaine N-ethyl bromide shows higher permeation (-5.93cm/s) despite having higher molecular weight.

5.5. Stability

The most important limiting factor involving in scale-up of phytopharmaceuticals is the stability of therapeutic entities. Phytochemicals undergo physical instability problems due to the presence of impurities and volatile components, variation in chemical composition, and microbial growth during storage. Various environmental factors such as altitude, temperature, nature of soil as well as harvesting and purification processes can cause alterations in the stability profile of phytochemicals. Apart from this, the stability of phytochemicals and their dosage forms often fluctuates during storage due to oxidation, hydrolysis, crystallization, emulsion breakdown, enzymatic deterioration and chemical reactions with additives & excipients. Temperature and moisture also play a major role in the quality and stability of phytopharmaceuticals. A 2 to 3-fold increase in the rate of chemical reaction is observed with every 10˚C elevation in temperature [187]. The presence of moisture and enzymes in phytochemicals during storage enhances the rate of hydrolysis and chemical degradation. Light is also an important factor impacting stability by generating free radicals.

6. NANOTECHNOLOGY DRIVEN TOPICAL PHYTOPHARMACEUTICALS WITH AUGMENTED PHARMACEUTICAL FEATURES

Nanotechnology is a multidisciplinary scientific area, which employs a diverse array of tools and techniques derived from engineering, physics, chemistry and biology [188,189]. Advancements in nanoscience and nanotechnology have made it possible to manufacture and characterize sub-micron bioactive carriers on a routine basis. The delivery of bioactives to target sites inside the body and their release behavior is directly affected by particle size[190]. Compared to micrometer-sized carriers, nanocarriers provide more surface area and have the potential to increase solubility, enhance bioavailability, improve controlled release and enable precision targeting of the entrapped material to a greater extent[191]. Advancements in science and technology led to a better understanding of disorders at molecular levels and helped in the development of therapeutically active molecules [192]. In comparison with synthetic molecules, phytochemicals are safe and display better activity in the management of chronic disorders [193]. The topical application of phytochemicals minimizes the occurrence of systemic toxicity associated with oral or parental administration. However, most of the phytochemicals exhibiting promising activity in the management of OA are not suitable for topical applications due to their limited bioavailability and stability issues. Interestingly, nanotechnology driven topical phytopharmaceuticals not only improve the dermatokinetic profile but also enhances the stability. Nanoscale-up can be used to create a microenvironment that helps in the stabilization of phytomolecules by preventing ionization. Conversely, the use of nano-enabled topical drug delivery systems containing phytomolecules in the management of OA is not well explored.

6.1. Self-assembled hyaluosomes amalgamated gel for the management of osteoarthritis

Hyaluosomes are nanodrug delivery systems containing elastic vesicles prepared using phospholipids, an edge activator, and hyaluronic acid (HA). Since HA is biodegradable, biocompatible, non-immunogenic, and non-

inflammatory in nature as well as exhibits a large water holding capacity due to which it can be used as a drug delivery carrier.

Recently, hyaluronic acid was explored as a vehicle in the development of a depot system for topical delivery. *El-Refaie et. al.* has prepared hyaluosomes containing lipoid S100 and tween 80 as edge activator, phospholipid and hyaluronic acid by thin-film hydration technique to achieve homogenous size distribution. As the concentration of HA increases from 0.2-1%, hyaluosomes displays higher drug entrapment efficiency. The incorporation of vesicles into the gel reduces the chances of aggregation and fusion process during storage. *Ex-vivo* skin permeation and deposition studies suggest that the permeation of hyaluronic acid into receptor fluid through the skin from hyaluosome and hyaluosome loaded gels were significantly higher compared to conventional aqueous dispersion, liposomes as well as liposomal gels. Apart from this, dermal localization was found to increase in hyaluosome loaded gel and liposomal HA gel with the increase in HA concentration (2 to 10 mg/ml). The enhancement in dermal localization and permeation may be due to the high hygroscopic property of HA which creates hydrophilic pathways. Gel core hyaluosomes (1% HA equivalent) shows higher dermal localization up to 4.3-folds compared to 1% HA gel, whereas minimal quantities (7.9-13.1 µg) of HA were found in joints after a single application for 6h. Interestingly, the application of 2% equivalent gel core hyaluosomes, twice a day for 48 h showed significantly higher dermal localization as well as enhanced penetration into joint tissues up to 6-folds [194].

6.2. Leech saliva extract encapsulated liposomal gel for knee osteoarthritis

Hirudo therapy (leech therapy) is used for the treatment of various diseases from ancient times due to their rare and mild side effects such as local itching associated with erythema. Initially, the saliva was collected from a starving leech (Hirudo medicinalis) belonging to the family, *Hirudinidae*. The amount of protein present in the saliva was processed through multistage filtration and centrifugation to remove the impurities. The quality and quantity of proteins in the salivary extract was determined using SDS-PAGE analysis and UV-spectrophotometer at 280nm. To enhance the stability and handling, the salivary extract was lyophilized using sucrose and fructose as a cryoprotectants. Liposomes were prepared by employing a thin-film hydration technique using herbal phospholipids (soybean lecithin) and 5% cholesterol having an average vesicle size of 92nm. The efficacy of patients treated with leech salivary extract, liposomal gel, and physiotherapy exercise for 30 days was compared with patients treated with physiotherapeutic exercise displaying approximately 50% reduction in pain while 50% enhancement in quality of life according to VAS and Lequesne questionnaires analysis. Thus, phytochemical loaded liposomal gels offers a potential strategy for the management of OA [196].

6.3. Topical delivery of diacerein loaded niosomal gel

The optimization of diacerein encapsulated niosomes was done by applying response surface methodology. To examine the effect of charge inducing agent, HLB (Hydrophilic-Lipophilic Balance) of surfactant and sonication time on vesicle size, entrapment efficiency, and cumulative drug release profile, Box-Behnken design (BBD) was employed. Diacerein encapsulated niosomes were prepared by employing thin-film hydration technique using stearyl amine as a charge inducer and cholesterol as a membrane stabilizer having vesicle size from 7.33µm to 23.72µm exhibiting lower PDI. The entrapment efficiency of the prepared niosomes was ranged from 9.52 to 58.43% and it displayed an inverse relationship with the concentration of charge inducing agents (0-10%). Drug loaded niosomes were amalgamated with various cellulosic derivatives in varying concentrations. *In-vitro* study

revealed that 3% methylcellulose (MC) and 3% HPMC gel release 78% and 80.3% of entrapped drug, respectively. Interestingly, diacerein entrapped niosomes amalgamated with 3% MC and 3% HPMC gel showed better oedema inhibition 34.52% and 37.66% in comparison to commercial gel (20.83%) at the end of 6h. Therefore, topical niosomes could be a promising approach to achieve higher therapeutic efficacy at lower concentrations while reducing the side effects [197].

6. REGULATORY CHALLENGES IN PHYTOPHARMACEUTICALS

Plant-based medicines are employed for healthcare since the earliest times of mankind. Despite the development of multiple synthetic molecules, phytomolecules are still engaged in the treatment of multiple chronic conditions. Phytochemicals are of great importance not only for pharmacological research or drug development but also as a starting material in API (Active Pharmaceutical Ingredient) synthesis. However, legislative control over the preparation and marketing of the herbal product has not been structured systematically to synchronize the sky rocketing in the demands [198].

The rules and regulations for the development of phytopharmaceuticals differ from nation to nation. Interestingly, the population residing in developing countries have great knowledge regarding folk medicine but due to a lack of efficacy related scientific piece of evidence [198]. International trade of herbal drug products is governed by international treaties such Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), which also regulates the worldwide trade of endangered or vulnerable species. Herbal goods are classified differently across the globe, with some of the most common categories are complimentary medicines, traditional medicine, dietary health supplements, over-the-counter medicines, while very few products are available as prescription medicine.

The most common regulatory challenges encountered in the commercialization of herbal products are related to quality control, safety, and efficacy assessment [199]. In contrast to conventional pharmaceutical preparations, herbal products involve multiple bioactive chemicals along with inactive components. Analysis and quantification of each chemical moieties present in a phytopharmaceutical is virtually impossible [200]. To overcome the quality control related hurdles, phytopharmaceuticals containing only active components from various plant extracts can be produced. However, such kinds of processes require an enormous workforce and capital investment. Apart from this, the quality of raw materials employed in the preparation of phytopharmaceutical impacts the safety and efficacy to a considerable extent. Usually, the quality of raw materials used in herbal product manufacturing is not only influenced by intrinsic or genetic elements but also by extrinsic factors such as environmental conditions, farming procedures, collection techniques, cultivation methods, etc [201]. The combination of all these parameters makes the quality control of herbal product raw materials a herculean task. In countries having regulated herbal medicine markets, WHO advises for the implementation of quality assurance and control measures for manufacturing and marketing to ensure its safety and efficacy [202]. Therefore, regulating the production and marketing of herbal drug products requires the collaboration between regulatory bodies, botanical institutions, and other major stake holders involved in the production and development.

7. FUTURISTIC APPROACHES AND CONCLUSION

All research hitherto has ushered in a new and exciting era of nanotechnology driven drug delivery cargo comprising phytoconstituents for OA treatment. OA, a multifactorial disorder, affects the whole joint involving

both central and peripheral sensitization resulting in arduous movement. Decades of research and effort have accounted a deep background on understanding the processes contributing to OA, yet a lot needs to be unboxed. This review summarizes 5 plant-based commercial dosage forms for the management of arthritic conditions and 179 bioactive compounds belonging to different classes of phytochemicals displaying promising activity against OA by inhibiting or modulating the effect on COX enzymes, MMP's and inflammatory cytokines. Development and progression of OA caused by various factors such as COX-2 expression on subchondral bone, secretion of inflammatory markers (TNF-α, IL-1β, and IL-6) in the synovium cavity and MMPs, ADAMTS & ADAM (metalloproteinases) induced extracellular matrix degradation.

Recent studies suggest that MMPs (MMP-13) plays a leading role in cartilage degradation. However, the use of available synthetic MMP inhibitors has been restricted since they display the development of musculoskeletal syndrome (MSS) owing to the high structural resemblance between MMPs. Interestingly, phytomolecules such as resveratrol, curcumin, and epigallocatechin-3-gallate demonstrated chondroprotective activity by indirect MMP inhibition with minimal side effects. Presently, very few phytochemicals are explored for the treatment of OA compared to rheumatoid arthritis (RA). There are some new research tools such as biolabel-led research pattern [203], chinmedomics [204] that can be used for quick discovery of mechanism and chemical basis in the management of OA. Apart from this, to improve the therapeutic efficacy while reducing the dose-dependent side effects of synthetic MMP inhibitors, it can be combined with phytomolecules. To lessen the systemic toxicity, nanotechnology driven topical phytopharmaceuticals such as nanoemulgels can be formulated as it shows higher absorption than other conventional topical dosage forms (**Figure 4**). Additionally, the association of phytomolecules with phospholipids (Phytosomes) offers a stable formulation for topical application with reliable absorption. For the optimization and development of phytopharmaceuticals, *in silico* tools such as Quality by Design (QbD), Artificial Neural Network (ANN) can be considered. Hence, the majority of phytochemicals have been proved as valuable clinical alternatives for OA treatment and warrant a laudable affair for further investigation. In addition, phytomolecules can be amalgamated with nanotechnology driven drug delivery systems to scale up topical phytopharmaceuticals for the management of OA.

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CONFLICT OF INTEREST

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Figure legends

Figure 1: Schematic representation of factors contribute to occurrence of oosteoarthritis. Osteoarthritis occurs due to ageing, mechanical stress on joints, and inflammation. Moreover, osteoarthritis accounts for 2-3% of morbidity and affect approximately 300 million people around the world.

Figure 2: Overview of pathophysiology of osteoarthritis. Osteoarthritis upregulates production of inflammatory mediators. The overexpression of A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) and aggrecan degradation molecules is responsible for the cartilage damage that later confirmed by stimulating IL-1β in OA chondrocyte and synovial fibroblast.

Figure 3: Overview of structure activity relation-ship (SAR) in representative phytomolecules. (i) The presence of electron-withdrawing groups such as the chloro group at 7th position enhanced the COX-2 selectivity in comparison to electron-donating groups in coumarins; (ii) The presence of a double bond at C_2-C_3 position of C ring plays an important role in Nrf_2 activation in flavonoids. (iii) Lignans are synthesized by the reduction of ferulic acid into coniferyl alcohol followed by oxidative dimerization to establish a linkage via β-carbon of C_3 side chain; (iv) Steroidal triterpenoids inhibit the proliferation of COX and MMP enzymes; and (v) To exhibit maximum inhibition of COX enzymes, the phenolic component should have a sterically free phenolic hydroxyl group in essential oils. EDG: Electron Donating Group.

Figure 4: Challenges associated with scale-up of phytopharmaceuticals are hindered bioavailability, poor aqueous solubility, unstable molecular structure, poor stability and deprived permeation. On the other hand, nanoscale-up (vesicular and particulate systems) can be used to create a microenvironment for stabilizing the phytomolecules.

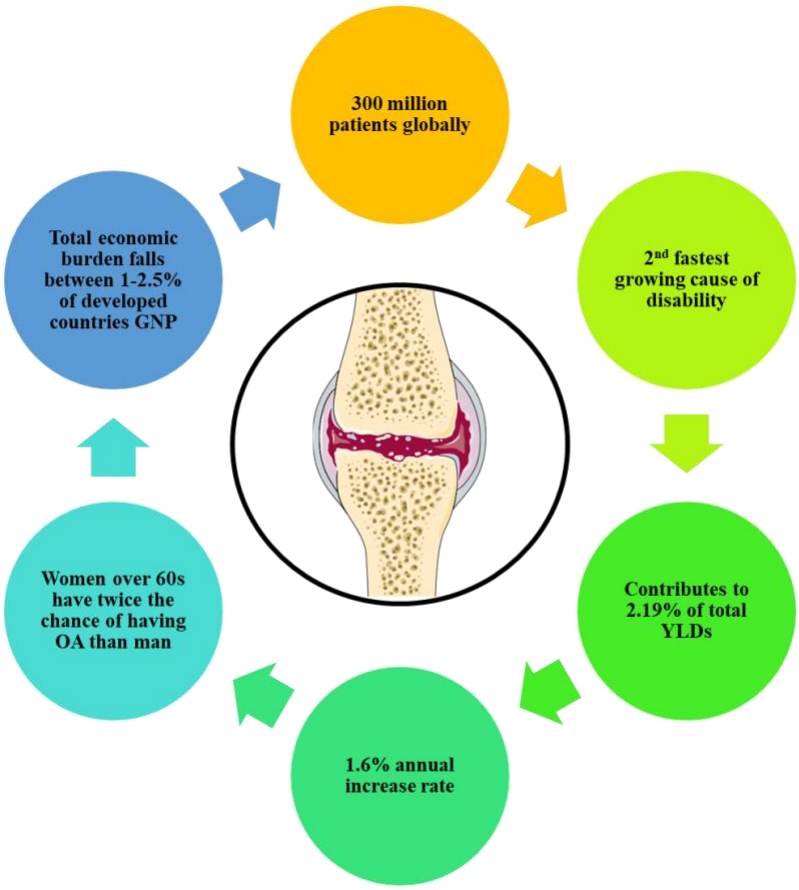

Figure 1

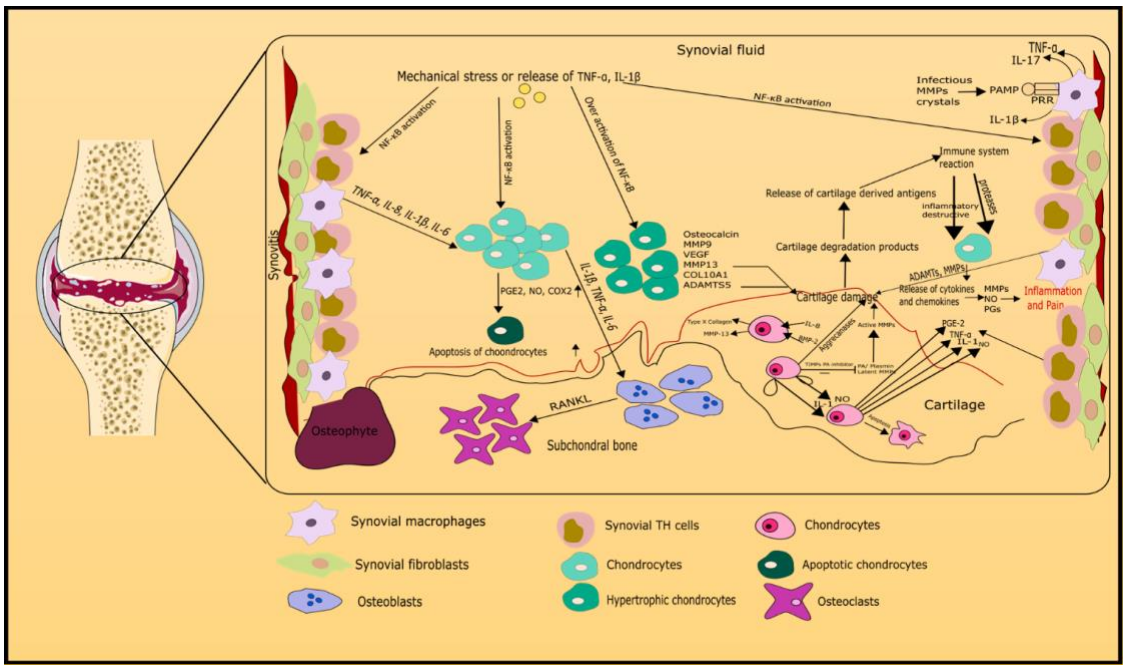

Figure 2

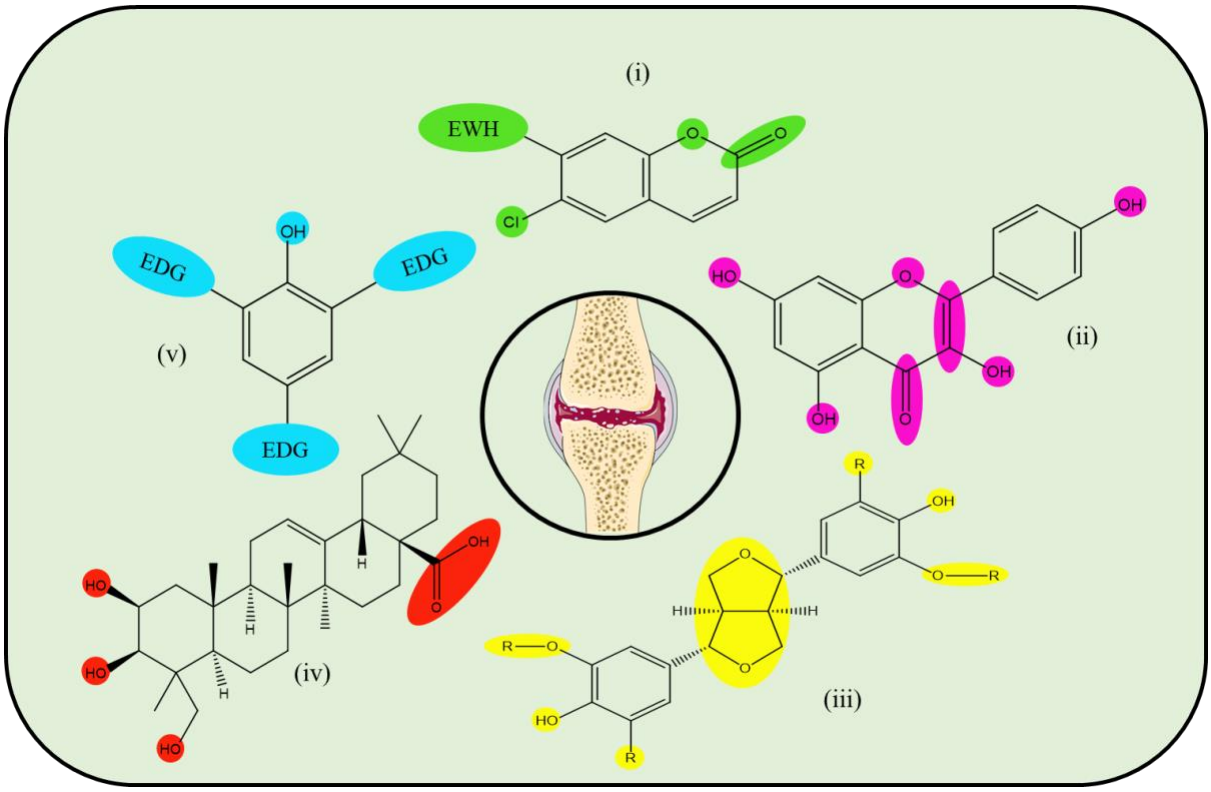

Figure 3

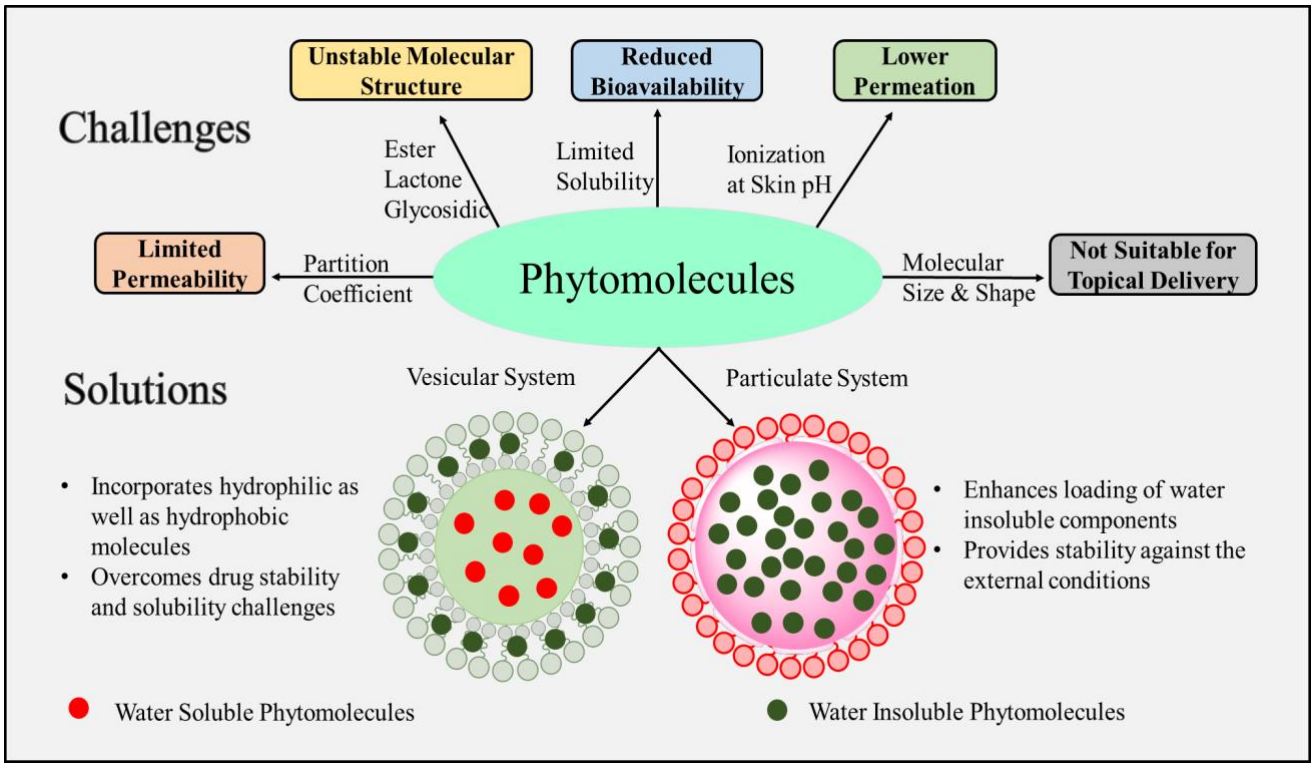

Figure 4