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Potentially effective natural drugs in treatment for the most common rheumatic disorder: osteoarthritis

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Abstract Osteoarthritis (OA) is a chronic condition in which imbalance between anabolic and catabolic mediators occurs leading to the destruction of homeostasis of articular cartilage. The current drugs in the management of OA can just alleviate symptoms. Hence, the research tendency toward exploration of novel sources has been grown up in order to achieve safe and efficacious drugs. Meanwhile, various components exist as novel natural drugs that may possess favorable properties for the management of OA. This review focuses on the most efficacious medicinal plants and their phytochemical agents, which have been consumed for the management of OA. Moreover, evaluation of their efficacy and molecular mechanisms of action are discussed based on numerous modern experimental investigations. More research is needed to develop therapeutic agents with disease-modifying properties to treat OA.

Keywords Osteoarthritis · Medicinal plant · Oxidative stress · Inflammation · Pro-inflammatory cytokine · Pain

Abbreviations

NO	Nitric oxide
LT-B4	Leukotriene-B4
iNOS	Inducible NO synthase
LPS	Lipopolysaccharide
12-LOX	12-Lipoxygenase
TNF-α	Tumor necrosis factor-alpha

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CYP P450	Cytochrome P450
Con A	Concanavalin A
MAPKs	Mitogen-activated protein kinase
COX1	Cyclooxygenase-1
PGE2	Prostaglandin-E2
HNE	Human neutrophil elastase
IFN-γ	Interferon-γ
IL-1β	Interloukine-1β
JNK	c-Jun N-terminal kinase
ERK	Extracellular signal-regulated kinase
NF-κB	Nuclear factor κB
MMP	Matrix metalloproteinases
GM-CSF	Granulocyte–macrophage colony-stimulating factor
PGN	Peptidoglycan
PLA2	Phospholipase A2
PHC	Primary human chondrocytes
IgG	Immunoglobulin G
CFA	Complete Freund's adjuvant
EPP	Ethyl phenylpropiolate
PMA	Phorbol 12-myristate 13-acetate
GABA	Gamma-Aminobutyric acid
5-HT	5-Hydroxytryptamine
TPA	12-*O*-tetradecanoylphorbol-13-acetate
MDA	Malondialdehyde
MPO	Myeloperoxidase
SOD	Superoxide dismutase
CAT	Catalase
GPx	Glutathione peroxidase
TNBS	2,4,6-Trinitrobenzene sulfonic acid
BALB/c	Inbred strain of mouse
TLR	Toll-like receptor
FGF	Fibroblast growth factor
NGF	Nerve growth factor
VEGF	Vascular epidermal growth factor
EGF	Epidermal growth factor

Introduction

Osteoarthritis (OA) is the most common type of arthritis, characterized by pain, stiffness, and loss of function in the joints. Although the etiology of OA is still unknown, epidemiologic reports and studies suggest a crucial role for both genetic and environmental factors in the causation of the disease. The fundamental aspect of OA pathogenesis is articular cartilage destruction caused by chronic inflammation [1–3]. OA is among the ten most disabling diseases in industrialized countries [4]. Prevalence studies showed that OA is strongly age-dependent, being less common before 40, but rising in frequency with age, such that most people older than 65 show some radiographic evidence of OA in at least one or more joints [5].

Various biological factors are involved in the pathogenesis of OA. Several anabolic and catabolic mediators play key roles in the homeostasis of articular cartilage, resulting in the progression of OA [3]. Pain is particularly important and is thought to be the most noticeable and disabling clinical symptom of OA [6].

Recently, several distinct molecular mechanisms that are possibly commensurate with OA pathogenesis have been identified. Although several pharmacotherapeutic choices that inhibit one or more processes in the pathogenesis of OA are under evaluation for their potential to alter the degenerative process, a complete cure for the disease has not yet been found. Hence, developing more effective therapies is an immediate and important challenge.

This review discusses the potential effects of herbal medicine on joint health based on cell, animal, and human studies along with the possible molecular mechanisms. For thousands of years, many ancient civilizations and cultures have used and refined herbal extracts for treating a variety of joint pains. Indeed, many of the antioxidant, anti-inflammatory, and pain analgesic drugs in our current pharmacopoeia have long established roots in ethnopharmacology. In this review, the most up-to-date information and trends in this area are highlighted. Additionally, we attempted to emphasize the mechanistic aspects targeting pathological pathways involved in OA.

Pathophysiological processes in osteoarthritis that could be favorably targeted by herbal medicines

Inflammation and synovitis

OA is characterized by limited intra-articular inflammation, inflammation of the synovium, and articular degeneration. Synovitis occurs in both the early and late phases of OA and is one of the main contributors to cartilage matrix destruction. Synovitis is associated with the progression of cartilage damage and also increased pain severity [7].

Inflammation in OA also affects the subchondral bone in the zone of calcified cartilage, which invades the deep hyaline cartilage layer. There is ample evidence suggesting a role of pro-inflammatory cytokines especially tumor necrosis factor (TNF) and interleukin-1β (IL-1β) in the inflammatory response of OA [8]. Pro-inflammatory cytokines such as IL-1, IL-8, and TNF-α can stimulate cyclooxygenase-2 (COX-2), and nitric oxide synthase (NOS), especially the inducible isoform of NOS (iNOS) expression. COX-2 and iNOS overexpression can cause overproduction of their products including NO and prostaglandin E2 (PGE2) [9, 10]. These cytokines can stimulate joint

damaging cytokines, including granulocyte–monocyte colony-stimulating factor and IL-6, released by macrophages and synoviocytes [9]. Moreover, activation of proteolytic enzymes, including matrix metalloproteinases (MMPs) and collagenases, promotes cartilage breakdown causing synovitis. Pro-inflammatory cytokines inhibit the synthesis of proteoglycans and collagen, increasing their degradation. Thus, cartilage degeneration creates a vicious circle further inducing synovial inflammation [11–13]. Furthermore, several studies highlight the contribution of TNF, IL-1β, and IL-8 in nociceptive pathways in OA by the production of eicosanoids and sympathetic amines [14].

Oxidative damage

"Reactive oxidative species" (ROS) is an inescapable consequence of vital processes, particulary aerobic metabolism. Any metabolic alteration in the production of ROS that exceeds their catabolism can lead to increased oxidant-derived tissue injury or oxidative stress [15, 16].

Several clinical and experimental studies document the important physiological role of oxidative stress in chondrocytes, i.e., chondrocytes are potent source of ROS [16]. There is ample evidence suggesting the role of ROS overproduction in inflammation signaling, pain nociception, and destruction of aging in osteoarthritic cartilage [3, 17]. Indeed, patients with chondral and meniscal lesions demonstrate increased levels of ROS including oxygen ions, superoxide radicals, peroxides, hydroxyl radicals, and hydrogen peroxides, which is originated from oxidative burst mediated by the NADPH oxidase system, in their synovial fluids [3, 16, 17]. Recent studies suggest the involvement of mechanical stress-induced ROS formation in the pathogenesis of OA. Furthermore, oxidative stress may play a crucial role in linking aging with OA [3, 16, 17].

On the other hand, extensive and multilayered antioxidant defense systems containing definite proteins of oxidative stress signaling pathways and antioxidative enzymes such as glutathione (GSH), catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) as well as redox-sensitive transcription factor which regulates redox homeostasis, nuclear factor erythroid 2-related factor 2 (Nrf2), are present in the human body [3, 16, 17, 38]. Furthermore, dietary intake might have a crucial role in the concentrations of antioxidants in the blood. It is also plausible that a high intake of dietary antioxidants may exert alleviating properties in OA [3, 11, 17].

Pain mediators

Cartilage degradation is often attended by pain and physical dysfunction. Arthritic pain due to OA is one of the most disabling symptoms among chronic arthritic conditions. Pain is the most noticeable and disabling clinical symptom of OA, often accompanied by less than optimal functional outcome with reduced quality of life [6]. A combination of sensory, affective, and cognitive processes reflecting impaired cellular mechanisms at both peripheral and central levels of the nervous system maybe at the root of the pain seen in OA [3, 18, 19]. Nociceptors are widely distributed throughout the joint structure including the joint capsule, ligaments, periosteum, and subchondral bone [20].

Damage of the joint cartilage and synovia influences nociceptors located throughout the joint. Peripheral afferent neurons are affected by injury. These triggers are transferred through dorsal root ganglion neurons to the cortical center for processing. This process causes symptomatic pain via central and peripheral sensitization [19, 21]. Moreover, chronic pain in OA may be perpetuated by non-nociceptive factors such as neuropathic component as the result of peripheral inflammation and central sensitization [22].

There is ample evidence suggesting the contribution of central and peripheral pathways in the OA pain mechanism. Indeed, intra-articular anesthetic injections in osteoarthritic hip and knee joints alleviate only 60–80 % of the pain present, depending on the affected joints [23, 24].

In some cases, impaired central mechanisms such as a dysfunction of the descending inhibitory control or an altered cortical processing of noxious information may also contribute to the pain present in OA [25].

Furthermore, mounting evidences suggest several mediators directly or indirectly contribute to the hyperalgesia in OA, which can be categorized into inflammatory mediators (TNF, IL-1, 6, 17, prostanoids and PGE2, NGF, EGF, VEGF, and FGF-2), signaling mediators (NF-κB, ERK1/2, JNK, TLRs, and iNOS), and proteases (MMP-1,3,9, and 13) [3, 6].

Herbal medicine

A large number of herbal medicines have traditionally been used for the management of OA. Many patients suffering from OA symptoms prefer herbal treatment. Traditional medicines all over the world encompass a wide range of herbal remedies in the healing of symptomatologies related to various disorders. Therefore, it is important to evaluate the safety and efficacy of herbal medicines and plant extracts that are taken orally or applied topically for the treatment for OA [26, 27]. In this regard, it would be useful to study the phytochemical active components of herbs and plants in order to develop potentially novel therapies for the treatment for OA. Our review was conducted to evaluate medicinal herbs considered anti-arthritic agents, collect evidence for their potential efficacy addressing when possible their pharmacological mechanisms in an effort to clarify their potential use for the management of OA in the scientific literature.

Table 1 Medicinal plants used traditionally for the treatment for OA

Scientific names	Family	Traditional name(s)
Achillea millefolium	Asteraceae	Bumadaran, Hazanbal
Acorus calamus	Acoraceae	Vaj, Agir torki
Allium sativum	Amaryllidaceae	Soam, Seer
Aloe spp	Asphodelaceae	Saber
Althaea officinalis	Malvaceae	Khatmi
Anethum graveolens	Apiaceae	Shebat, Shevid
Boswellia carterii and B. serrata	Burseraceae	Kondor
Capparis spp	Capparaceae	Kabar, Khavarak
Cassia spp	Fabaceae	Folus, Khiar-e-shanbar
Cinnamomum zeylanicum and C. cassia	Lauraceae	Dar-e-chini, Ghorfe
Colchicum autumnale	Colchicaceae	Surenjan, Gol-e-hasrat
Commiphora myrrha	Burseraceae	Morr
Curcuma zedoaria	Zingibaraceae	Jadvar
Elaeagnus angustifolia	Elaeagnaceae	Zaghum, Senjed
Hypericum perforatum	Hypericaceae	Hofarighun, Alafe chae
Linum usitatissimum	Linaceae	Katan
Matricaria chamomilla	Asteraceae	Babunaj, Babune
Myrtus communis	Myrtaceae	Mourd, Aas
Nigella sativa	Ranunculaceae	Shuniz, Siah dane
Phyllanthus emblica	Phyllanthaceae	Amole
Pistacia lentiscus and P. atlantica	Anacardiaceae	Mastaki, Saghez (oleo-gum resin)
Ruta graveolens	Rutaceae	Sodab
Sambucus ebulus	Adoxaceae	Khamman-e-kabir, Aghti-e-siah
Zingiber spp.	Zingiberaceae	Zanjabil

As shown in Table 1, various herbs have been traditionally used for OA. Also, their plant family and vernacular names are listed. Following are the molecular and biological mechanisms of action of medicinal plants and their active phytochemical agents.

Achillea millefolium

A. millefolium demonstrates in vitro anti-inflammatory activity by decreasing HNE and inhibiting MMP-2 and 9 (Table 2) [28]. *A. ageratum* and *A. santolina* exhibit anti-inflammatory activity in vivo by decreasing IL-6, MPO level, and suppressing neutrophil migration into inflamed tissue [29, 30]. *A. fragrantissima* shows anti-inflammatory activity by decreasing MMP-9 levels and inhibiting IL-1β, COX-2, NO, iNOS, and TNFα production [31]. Stigmasterol, beta-sitosterol, and dicaffeoylquinic acids are the main active components [28, 30].

Acorus calamus L

The leaves show anti-inflammatory activity in vitro by decreasing IL-8 and IL-6 with inhibition of NF-κB production. Furthermore, the roots exhibited analgesic activity by inhibiting PG and bradykinin production [32, 33]. The anti-inflammatory activity of *A. gramineus* is attributed to the reduction of NO activity, inhibiting iNOS expression. Surinamensinols and acoramol are the responsible compounds [32].

Allium sativum

A. sativum demonstrates anti-inflammatory activity in vitro by decreasing various pro-inflammatory mediators [34]. *A. flavum* showed anti-inflammatory action by decreasing COX-1 and 12-LOX levels [35]. Glucopyranosides, allivictoside, various phenolics, and some allyl derivative compounds are responsible for their anti-inflammatory action [36].

Aloe spp

Anti-inflammatory function of *A. barbadensis* is attributed to the inhibition of TNF-α and IL-1β level [37]. Researchers have shown that *A. vera* possesses anti-inflammatory activity by decreasing PLA2 and MMP-9 level [38–40].

Althaea officinalis

A. officinalis and *A. rosea* exhibit anti-inflammatory and analgesic activities in animal models [41, 42]. Furthermore,

A. rosea demonstrated anti-inflammatory action by blocking PGE release from inflamed tissue [42].

Anethum graveloens

The flowers exhibited anti-inflammatory activity in vitro by decreasing NO, iNOS, IL-1β, IL-6, and NF-κB activity. Moreover, the seeds showed similar action in animal models, as well as anti-nociceptive activity [43, 44].

Boswellia carterii and B. serrata

B. carterii decreases CFA-induced edema by suppressing TNF-α and IL-1β levels in animal models. An analgesic action has been proven [45]. In addition, an anti-inflammatory effect of *B. serrata* by suppressing pro-inflammatory mediators has been reported with 12-ursene 2-diketone being the responsible compound [46]. In a clinical trial, administration of oleo-gum resin of *B. serrata* in patients with OA of the knee resulted in reduction in knee pain and swelling along with improvement of knee flexion and walking distance as compared to placebo; here, boswellic acid derivatives seem the main biological components [47].

Capparis spp

C. spinosa can inhibit CFA-induced arthritis in rats. Table 3 shows the main active constituents responsible for this function [48, 49]. Also, *C. ovata* suppresses paw edema by decreasing COX in mice. Moreover, its analgesic activity has been confirmed in an animal model [50, 51].

Cassia spp

C. alata decreases CFA-induced arthritis with the suppression of cartilage degradation in the knee joint, decreasing swelling and suppressing leukocyte infiltration in the synovial fluid in an animal model [52]. *C. siamea and C. occidentalis* demonstrate anti-inflammatory activity in mice by decreasing MDA [53]. Moreover, the analgesic activity of *C. siamea* has been proven in an animal model [54].

Cinnamomum zeylanicum and C. cassia

C. cassia demonstrates anti-inflammatory activity in vitro and in vivo by suppressing pro-inflammatory mediators and enhancing antioxidant enzymes [55, 56]. Furthermore, *C. zeylanicum* suppresses paw edema and CFA-induced arthritis in animals [57].

Colchicum autumnale

C. luteum shows anti-inflammatory activity by suppressing TNF-α, IL-6, and IL-1β. It also inhibits CFA- and formaldehyde-induced arthritis in rats [58, 59].

Commiphora myrrha

It shows anti-inflammatory activity suppressing PGE2 and NO production in animal models. Moreover, its analgesic action has been proven in vivo. Table 3 shows the possible biological active constituents [60]. *C. mukul* demonstrates anti-inflammatory activity by decreasing IFN-γ, IL-12, TNF-α, IL-1β, and NO level [61].

Curcuma zedoaria

The rhizomes possess anti-inflammatory properties as well as anti-arthritis activity with inhibition of joint swelling in animal models, with furanodiene and furanodien one being the active components [62, 63]. *C. comosa* shows anti-inflammatory activity by suppressing IL-1β, TNF-α, and NF-κB level; here, the diarylheptanoids are the effective compounds [64].

Elaeagnus angustifolia

An anti-inflammatory and analgesic function of these fruits has been demonstrated in animal models [65]. The anti-inflammatory potential of *E. oldhamii* seems to be by suppressing NO, IL-1β, IL-6, TNF-α, and COX-2 level [66].

Hypericum perforatum

An anti-inflammatory activity of the crude extract with its active components being pseudohypericin, amentoflavone, quercetin, hypericin, hyperoside, epicatechin, and chlorogenic acid has been proven in in vitro and in vivo studies; the potential-related mechanism seems suppression of various pro-inflammatory mediators [67–69]. In addition, Sánchez-Mateo et al. [70] reported that *H. reflexum* possesses analgesic activity in vivo as well.

Linum usitatissimum L

The seeds exhibit analgesic action. They suppress inflammation by reducing COX and LOX. Kaithwas et al. reported that the anti-arthritic effects of the plant and its active component, α-linolenic acid, are due to diminishing joint edema by decreasing PGE2, LT-B4 in animal models [71, 72].

Matricaria chamomilla

An analgesic and peripheral neuropathy inhibiting function of the plant has been documented in animal models [73]. In a clinical trial on patients with OA, the plant demonstrated inhibition of pain of the knee joint with decreased disease severity in comparison with placebo [74].

Myrtus communis

Its anti-inflammatory activity in vitro is by suppressing pro-inflammatory mediators. It also demonstrates analgesic and anti-inflammatory action through suppressing MPO, TNF-α, and IL-6 activity and leukocyte migration in mice and rats [75–77].

Nigella sativa

The seeds show anti-inflammatory and analgesic properties in vivo [78]. In a clinical study of patients with rheumatoid arthritis, the seed oil showed significant improvement of disease activity score, number of swollen joints, and duration of morning stiffness [79].

Phyllanthus emblica

The fruits exhibit suppressing action on animal inflammation [80]. In addition, *P. amarus* shows an anti-inflammatory effect by diminishing various pro-inflammatory cytokines [81]. It also inhibits allodynia and neuropathic pain with a decrease in MPO levels [82].

Pistacia lentiscus and P. atlantica

P. integerrima shows analgesic activity in animals [83]. The anti-inflammatory action of *P. lentiscus* is through the reduction in TNF-α and IL-6 production and leukocyte migration into inflamed tissue [84]. Moreover, *P. terebinthus* shows anti-inflammatory action by decreasing LT-B4 production; masticadienonic acid, masticadienolic acid, and morolic acid are the active phytochemical agents [85].

Ruta graveolens

Its anti-inflammatory activity is by the suppression of NO, iNOS, and COX-2; rutin is the active chemical agent [86]. Ratheesh et al. reported that the plant has beneficial activity on arthritis and edema via suppressing COX-2,5-LOX and MPO, elevating antioxidant performance; polyphenolic and alkaloid fractions are the main phytochemicals [87, 88].

Sambucus ebulus

Roots show anti-inflammatory activity in rats. In addition, rhizomes may have an analgesic potential in an animal model [89].

Zingiber spp

Z. zerumbet demonstrates an anti-inflammatory action by suppressing COX-2, iNOS, NO, and PGE2 in vitro, and in animal models, Zerumbone, 3-O-methyl kaempferol, kaempferol-3-O-(2,4-di-O-acetyl-α-l-rhamnopyranoside), and kaempferol-3-O-(3,4-di-O-acetyl-α-l-rhamnopyranoside) are the main phytoconstituents [90]. Khalid et al. reported an analgesic effect of *Z. zerumbet* by suppressing protein kinase C and the glutamatergic system in animals [91]. Moreover, efficacy of *Z. officinale* in the management of OA in human has been confirmed. Daily intake of capsules of *Z. officinale* extract in patients did not resulted in severe toxicity, and the only adverse event was commonly mild gastrointestinal disorders [97, 98].

Conclusions

Osteoarthritis, the most common musculoskeletal disorder, torments millions of people all over the world, resulting in chronic pain, along with a reduced quality of life, accompanied by elevated health costs. Presently, there is no effective treatment for OA, much less a cure. Currently, we mainly aim at alleviating symptoms [92]. Research has demonstrated that glucosamine and chondroitin sulfate can stimulate proteoglycan synthesis and inhibit proteolytic enzymes, so decrease cartilage lesion. However, in a large study, there was no difference between them and placebo in alleviating pain and functional improvement [4]. There is a lot of ongoing research to investigate newer therapies for OA, including the exploration of medicinal plants in an effort to isolate possible active ingredients that may have anti-arthritic properties. Herbal medicaments are much less expensive, may be more tolerable and widely available, having hopefully fewer side effects as compared to synthetic prescription drugs [27]. A wide range of herbal medicines have been traditionally used for the management of OA. Some scientific evidence suggests that natural medicaments may benefit the management of OA. Their anti-osteoarthritic effects seem to be mediated by the suppression of oxidative stress (i.e., iNOS, NO); cartilage degradation by destructive metalloproteinases (e.g., MMP-3, MMP-9); the downregulation of inflammatory cytokines such as IL-12, IL-2, IL-8, TNF-α, IL-1α, IL-6, IL-8, IFN-γ, and NF-κB; and their antioxidant (e.g., catalase, SOD, and GPx), analgesic, and anti-nociceptive

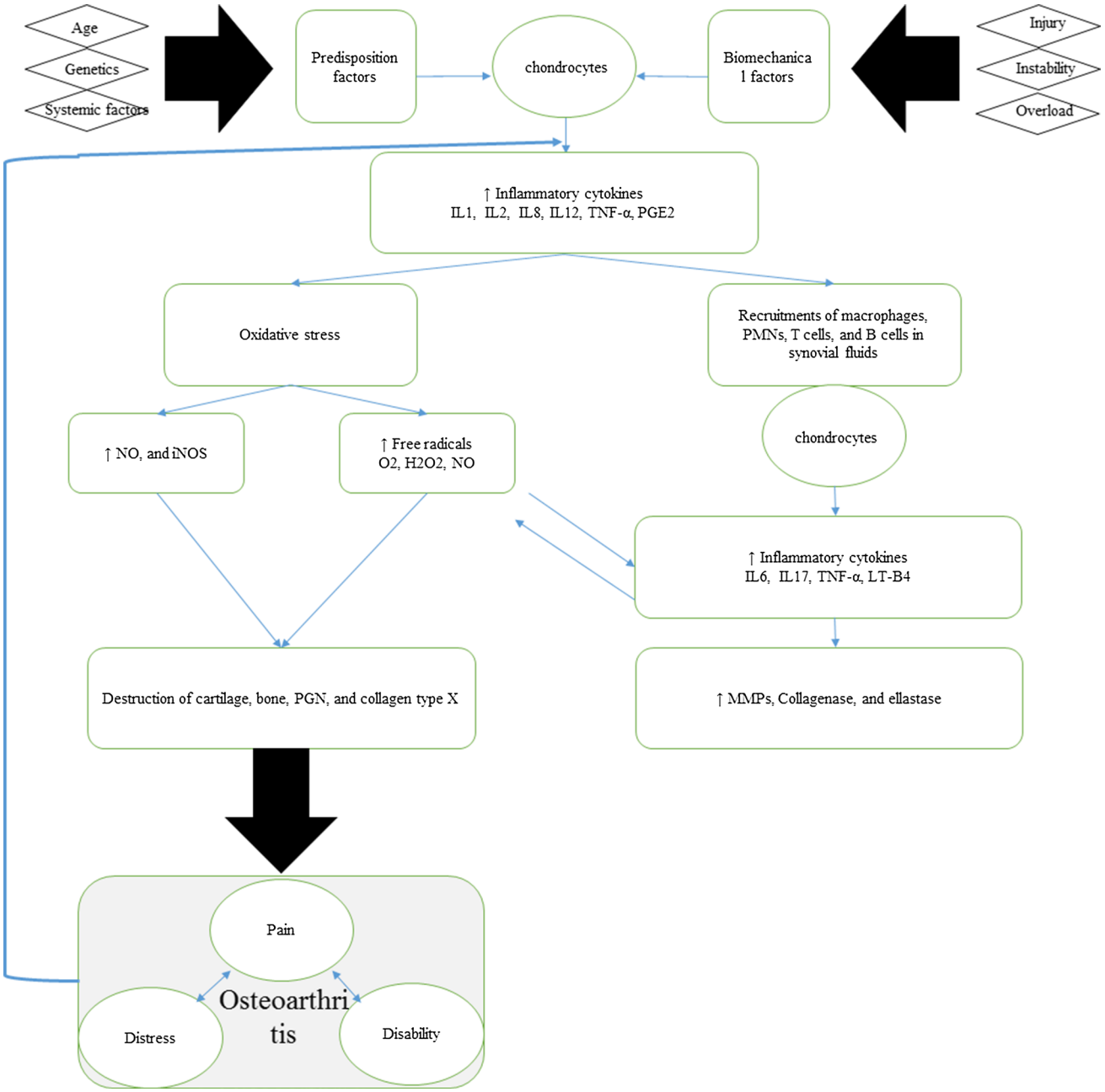

Fig. 1 Possible biochemical pathways and mechanisms in the pathogenesis of OA where medicinal plants can have an effect

properties. Figure 1 illustrates the possible biochemical mechanisms of medicinal plants and their phytochemicals. Various in vitro and in vivo research studies support the efficacy of these natural products on OA. Nevertheless, only 5 clinical trials have been performed for the evaluation of the effectiveness, including a trial on *B. serrata,* another on *M. chamomilla,* two trials on *Z. officinale*, and the last one using *N. sativa* (Table 4). A 8-week randomized double-blind placebo-controlled trial on 30 patients with OA of the knee revealed beneficial effect of *B. serrata* oleo-gum resin by reduction in knee pain and frequency of the knee joint swelling along with improvement of knee flexion and walking distance significantly in comparison with placebo group ($P < 0.001$) [47]. In a 6-week placebo-controlled double-blind crossover trial on 30 women and 12 men with OA of the knee reported by Soltanian et al. [74], *M. chamomilla* ointment demonstrated amelioration of pain of knee joint in primary knee OA patient as well as alleviation of the severity of disease-associated pain significantly in comparison with placebo

Table 2 In vitro studies of medicinal plants used in the treatment for OA

References	Active constituent	Result	Part	Plant
[31]	–	Anti-inflammatory activity by ↓NO, ↓IL-1β, ↓TNFα, ↓MMP-9, ↓COX-2, and ↓iNOS	Aerial part	*Achillea fragrantissima*
[28]	Flavonoids and dicaffeoylquinic acids	Anti-inflammatory activity via ↓HNE, ↓MMP-2, and 9	Aerial part	*Achillea millefolium*
[32]	–	Anti-inflammatory activity by ↓IL-8, ↓IL-6, ↓NF-κB	Leaves	*Acorus calamus L.*
[93]	Surinamensinols A, B, and acoramol	Anti-inflammatory activity via ↓NO activity and ↓iNOS expression	Rhizomes	*Acorus gramineus*
[35]	Phenolic compounds including ferulic, p-coumaric, caffeic, p-hydroxybenzoic, vanillic, protocatechuic and syringic acid, rutin, quercetin-3-O-glucoside, and kaempferol-3-O-glucoside	Anti-inflammatory activity via ↓COX-1 and ↓12-LOX	Aerial parts and bulb	*Allium flavum* L.
[34]	Allyl amino acid derivatives and allyl sulfides and flavonoids	Anti-inflammatory activity by ↓IL-12, ↓IL-8, ↓TNF-α, ↓IL-1α, ↓IL-6, ↓IL-8, ↓IFN-γ, and ↓IL-2	Bulb	*Allium sativum*
[36]	Allivictoside B, F, 3-O-β -D-glucosyl-7-O- β -D-(2-O-feruloyl) glucosylkaempferol and quercetin-3-O-β-D-glucopyranoside	Anti-inflammatory activity by ↓NO production	Leaves	*Allium victorialis*
[37]	–	Anti-inflammatory activity via ↓TNF-α and ↓IL-1β	Leaves/inner gel component	*Aloe barbadensis Miller*
[38]	–	Anti-inflammatory activity by ↓PLA2	Leaf skin	*Aloe vera*
[39]	–	Anti-inflammatory activity via ↓MMP-9	Gel	
[43]	–	Anti-inflammatory activity via ↓NO, ↓iNOS, ↓IL-1β, ↓IL-6, and ↓NF-κB activity	Flower	*Anethum graveloens*
[46]	12-ursene 2-diketone	All fractions showed anti-inflammatory activity by ↓TNFα, ↓IL-1β, ↓IL-6, ↓NO, and ↓iNOS	Oleo-gum resin	*Boswellia serrata*
[55]	Cinnamic aldehyde, cinnamic alcohol, and cinnamic acid	Anti-inflammatory activity by ↓NO, ↓TNF-α, ↓PGE2, ↓iNOS, ↓COX-2, ↓NF-κB	Bark/essential oils	*Cinnamomum cassia*
[61]	Guggulsterol	All extracts showed anti-inflammatory activity by ↓IFN-γ, ↓IL-12, ↓TNF-a, ↓IL-1β, and ↓NO	Oleo-gum resin/	*Commiphora mukul*
[64]	Diarylheptanoids: 5-hydroxy-7-(4-hydroxyphenyl)-1-phenyl-(1E)-1-heptene and 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-phenyl-(1E)-1-heptene	Both extract showed anti-inflammatory activity via ↓IL-1β, ↓TNF-α and ↓NF-κB	Rhizome	*Curcuma comosa*
[67]	Pseudohypericin, amentoflavone, quercetin, and chlorogenic acid	Anti-inflammatory activity by ↓PGE2, ↓NO, ↓IL-6, ↓TNF-α, ↓IL-1β, and ↓COX-2	Flowering tops	*Hypericum perforatum*
[68]	Amentoflavone, hyperforin, and pseudohypericin	Anti-inflammatory activity by ↓PGE2	Flowering tops	
[75]	Myrtucommulone and semimyrtucommulone	Anti-inflammatory activity via ↓5-LOX, ↓COX-1 ↓mobilization of Ca^{2+} in PMN leukocytes, ↓formation of reactive oxygen species, and ↓release of leukocyte elastase level	Leaves	*Myrtus communis*
[81]	–	Both extract showed anti-inflammatory activity by ↓NO ↓TNF-α, ↓iNOS, ↓COX-2, ↓NF-κB, ↓IL-1β, ↓IL-10, ↓INF-γ ↓TNF-α, and ↓PGE2	Fruits	*Phyllanthus amarus*
[86]	Rutin	Anti-inflammatory activity by ↓NO, ↓iNOS, and ↓COX-2	Whole plant	*Ruta graveolens L.*
[90]	Zerumbone, 3-O-methyl kaempferol, kaempferol-3-O-(2, 4-di-O-acetyl-α-l-rhamnopyranoside), and kaempferol-3-O-(3,4-di-O-acetyl-α-l-rhamnopyranoside)	Anti-inflammatory activity via ↓COX-2, ↓iNOS, ↓NO, and ↓PGE2. Zerumbone and 3-O-methyl kaempferol showed the most activity	Rhizome	*Zingiber zerumbet*

ND not determined, *NO* nitric oxide, *IL-1β* interleukin-1β, *TNF-α* tumor necrosis factor-alpha, *MMP-9* matrix metalloproteinases-9, *COX1* cyclooxygenase-1, *iNOS* inducible NO synthase, *LPS* lipopolysaccharide, *HNE* human neutrophil elastase, *NF-κB* nuclear factor κB, *PGN* peptidoglycan, *LOX* lipoxygenase, *IFN-γ* interferon- γ, *PLA2* phospholipase A2, *IgG* immunoglobulin G, *MAPKs* mitogen-activated protein kinase, *CYP P450* cytochrome P450, *JNK* c-Jun N-terminal kinase, *ERK* extracellular signal-regulated kinase, *LT-B4* leukotriene-B4, *PGE2* prostaglandin-E2, *PMA* phorbol 12-myristate 13-acetate, *TGF-β* transforming growth factor-β, *PMN* polymorphonuclear

Table 3 In vivo studies of medicinal plants used for the treatment for OA

References	Active constituents	Result	Method	Part	Plant
[94]	Stigmasterol and β-sitosterol	↓Ear edema by ↓MPO and ↓neutrophil migration into inflamed tissue	TPA-induced ear edema	Aerial part	*Achillea ageratum*
[29]	–	Methanol extract showed ↓paw edema and hyperalgesia by ↓serum IL-6	CFA-induced paw edema	Aerial part	*Achillea santolina*
[33]	–	Analgesic activity with ↓writhing response via ↓PG and ↓bradykinins	Acetic acid-induced writhing test	Roots	*Acorus calamus L.*
[95]	–	↓Vascular permeability	Acetic acid-induced vascular permeability	Bulb	*Allium ascalonicum*
[41]	–	↓Edema in both models	Carrageenan- and formalin-induced paw edema	Flower	*Althaea officinalis*
[42]	–	Analgesic activity with ↓twisting and ↑tail flick latency	Acetic acid-induced mice twisting and rats tail flick tests	Flower	*Althaea rosea L.*
[42]	–	↓Permeability of abdominal capillaries, ↓paw edema in all models by ↓PGE level	Acetic acid-induced capillary permeability and carrageenin- and dextran-induced paw edema	Flower	
[44]	–	Anti-nociceptive with ↓paw licking time	Formalin-induced paw licking time	Seed	*Anethum graveolens*
[44]	–	↓Ear edema	Xylene-induced ear edema	Seed	
[45]	–	↓Paw edema by ↓TNF-α and ↓IL-1β	CFA-induced paw edema	Oleo-gum resin	*Boswellia carterii*
[45]	–	Anti-nociceptive activity with ↑paw withdrawal time	Paw withdrawal latency test	Oleo-gum resin	
[50]	–	↓Paw edema by ↓COX in both model	Carrageenan- and PGE2-induced paw edema	Buds and fruits	*Capparis ovata*
[51]	–	Analgesic activity with ↑tail immersion latency, ↑hot plate reaction time and ↓writhing response	Tail immersion, hot plate and acetic acid-induced writhing tests	Fruits	
[49]	P-hydroxy benzoic acid, 5-(hydroxymethyl) furfural, bis(5-formylfurfuryl) ether, daucosterol, α-D-fructofuranosides methyl, uracil and stachydrine	Fraction eluted by ethanol–water 50:50 showed excellent anti-arthritic activity	CFA-induced arthritis	Fruits	*Capparis spinosa L.*
[52]	–	↓Arthritis with ↓cartilage degradation in femoral head of knee joint, ↓swelling and ↓leukocyte of synovial fluid	CFA-induced arthritis	Leaf	*Cassia alata*
[53]	–	↓Paw edema by ↓MDA in tissue	Carrageenan-induced paw edema	Whole plant	*Cassia occidentalis*
[54]	Triterpenes, flavonoids, anthraquinones and phytosterols	Both extract showed analgesic activity with ↑hot plate reaction time	Hot plate test	Stem bark	*Cassia siamea*
[54]	Triterpenes, flavonoids, anthraquinones and phytosterols	Both extract demonstrated ↓paw edema	Carrageenan-induced paw edema	Stem bark	

Table 3 continued

References	Active constituents	Result	Method	Part	Plant
[55]	Cinnamic aldehyde, cinnamic alcohol, cinnamic acid, and coumarin	↓Paw edema by ↓NO, ↓TNF-α, ↓PGE2, ↓MPO, ↓NF-κB, ↑catalase, ↑SOD, and ↑GPx	Carrageenan-induced paw edema	Essential oils of bark	*Cinnamomum cassia*
[57]	Procyanidine A and polyphenols	↓Paw edema and ↓arthritis by significant reversal of damage ankle diameter, arthritic score and serum C-reactive protein	Carrageenan-induced paw edema and CFA-induced arthritis	Bark	*Cinnamomum zeylanicum*
[58]	–	↓Paw edema, ↓granuloma formation by ↓TNF-α, ↓IL-6, and ↓IL-1β	Carrageenan-induced paw edema, cotton pellet-induced granuloma formation	Corms	*Colchicum luteum*
[58]	–	↓Arthritis and ↓joint swelling in both model by ↓TNF-α, ↓IL-6, and ↓IL-1β	CFA- and formaldehyde-induced arthritis	Corms	
[60]	2-Methoxy-8,12-epoxygermacra-1 7,11-trine-6-one, 2-methoxy-5-acetoxy-furanogermacr-1 en-6-one, myrrhone, sandaracopimaric acid, abietic acid, dehydroabietic acid, mansumbinone	Anti-nociceptive activity with ↓writhing response and ↑hot plate reaction time	Acetic acid-induced writhing and hot plate test methods	Oleo-gum resin	*Commiphora myrrha*
[60]	2-Methoxy-8,12-epoxygermacra-1 7,11-trine-6-one, 2-methoxy-5-acetoxy-furanogermacr-1 en-6-one, myrrhone, sandaracopimaric acid, abietic acid, dehydroabietic acid, mansumbinone.	↓Paw edema by ↓PGE2 and ↓nitrite in both model	Carrageenan- and formalin-induced paw edema	Oleo-gum resin	
[62]	Sesquiterpenes, furanodiene, and furanodienone	↓Edema of ear that its effect is comparable to indomethacin	TPA-induced ear edema	Rhizomes	*Curcuma zedoaria*
[63]	–	↓Arthritis and ↓swelling in ankle joint	CFA-induced monoarthritis	Root	*Curcuma zedoaria*
[65]	Flavonoids, terpenoids and cardiac glycosides	Analgesic activity with ↓paw licking time and ↑tail flick latency	Formalin-induced paw licking test and tail flick model	Fruits and endo-carp	*Elaeagnus angustifolia*
[65]	Flavonoids, terpenoids, and cardiac glycosides	↓Paw edema	Formalin-induced paw edema	Fruits and endo-carp	
[96]	–	Anti-nociceptive activity with ↓writhing response and ↑hot plate reaction time dose-dependently	Writhing test and hot plate test	Fruit and seeds	
[66]	–	↓Paw edema via ↓NO, ↓IL-1β, ↓IL-6, ↓TNF-α, and ↓COX-2	Carrageenan-induced paw edema	Leaf	*Elaeagnus oldhamii*
[69]	Hyperoside, isoquercitrin, rutin, (−) -epicatechin and hypericin	↓Capillary permeability	Acetic acid-induced capillary permeability	Aerial part	*Hypericum perforatum*
[70]	–	Anti-nociceptive activity with ↓writhing response, ↓paw licking time and ↑tail flick latency	Acetic acid-induced writhing, formalin-induced paw licking and tail flick test	Aerial part	*Hypericum reflexum L*

Table 3 continued

References	Active constituents	Result	Method	Part	Plant
[72]	–	Analgesic activity with ↓writhing responses and ↑tail immersion latency	Acetic acid-induced writhing and tail immersion tests	Seeds	*Linum usitatissimum L*
[72]	α-Linolenic acid	↓Inflammation in all models by ↓COX and ↓LOX	PGE2-, LT-, histamine-, bradykinin-, and arachidonic acid-induced inflammation	Fixed oil of seeds	
[71]	α-Linolenic acid	↓Joint edema by↓PGE2, ↓LT-B4, and ↓Secondary lesions in CFA-induced arthritis	Turpentine oil-induced joint edema and formaldehyde- and CFA-induced arthritis	Fixed oil of seeds	
[73]	–	Analgesic activity with ↓cisplatin-induced pain, ↓paw licking time and its effect is comparable to morphine	Cisplatin-induced peripheral neuropathy and formalin-induced paw licking tests	Aerial part	*Matricaria chamomilla*
[76]	–	Topical administration of essential oil showed ↓ear edema and ↓granuloma formation via ↓MPO activity, ↓leukocyte migration, ↓TNF-α and ↓IL-6 level	Croton oil- induced ear edema and cotton pellet-induced granuloma	Essential oil of aerial parts	*Myrtus communis*
[77]	Tannins, alkaloids, and flavonoids	Both extract showed analgesic activity with ↑hot plate reaction time and ↓writhing responses	Hot plate and acetic acid-induced writhing tests	Aerial parts	
[78]	Polyphenol	Analgesic activity with ↓writhing responses, ↓paw licking time but it was not effective in tail flick test	Acetic acid-induced writhing, formalin-induced paw licking, and tail flick tests	Seed	*Nigella sativa*
[78]	Polyphenol	↓Edema just in carrageenan-induced paw edema model	Carrageenan-induced paw edema and croton oil-induced ear edema	Seed	
[82]	Lignans	↓Allodynia and ↓neuropathic pain by ↓MPO	CFA-induced allodynia and partial ligation of sciatic nerve-induced neuropathic pain	Aerial part and leaves	*Phyllanthus amarus*
[80]	–	↓Paw edema and ↓peritonitis by ↓protein level of the peritoneal exudates	Carrageenan-induced rat paw edema and acetic acid-induced peritonitis in mice	Fruit	*Phyllanthus emblica*
[83]	–	Analgesic activity with ↓abdominal constrictions and ↓paw licking time	Acetic acid-induced abdominal constriction and formalin-induced paw licking tests	Leaves and galls	*Pistacia integerrima*
[84]	–	↓Paw edema and ↓granuloma formation via ↓TNF-α, ↓IL-6 production and, ↓leukocyte migration to inflamed tissue	Carrageenan-induced paw edema and cotton pellet-induced granuloma	Essential oil of oleo-gum resin	*Pistacia lentiscus* L.
[85]	Masticadienonic acid, masticadienolic acid, and morolic acid	↓Ear inflammation and ↓paw edema via ↓LT-B4 production in PMN leukocytes	TPA-induced mouse ear inflammation and PLA2-induced rat paw edema	Galls	*Pistacia terebinthus*
[87]	–	↓Arthritis and edema by ↓COX-2 and ↓MPO, and its effect is higher than indomethacin	CFA-induced arthritis	Aerial part	*Ruta graveolens*
[88]	Polyphenolic and alkaloid fractions	↓Paw edema and ↓arthritis by ↓COX-2, ↓5-LOX and improvement of antioxidant function: ↓lipid peroxidation, ↓MPO and ↑antioxidant enzymes	Carrageenan-induced paw edema and CFA-induced arthritis	Aerial part	

Table 3 continued

References	Active constituents	Result	Method	Part	Plant
[89]	Flavonoids, steroids, glycosides, and tannins	Analgesic activity with ↓paw licking time and ↑tail flick latency	Formalin-induced paw licking and tail flick tests	Rhizome	*Sambucus ebulus*
[89]	Flavonoids and steroids	↓Paw edema	Formalin-induced paw edema	Rhizome	
[90]	Zerumbone, 3-O-methyl kaempferol, kaempferol-3-O-(2, 4-di-O-acetyl-α-l-rhamnopyranoside) and kaempferol-3-O-(3,4-di-O-acetyl-α-l-rhamnopyranoside)	↓Paw edema by ↓COX-2 and ↓iNOS	Carrageenan-induced paw edema	Rhizomes	*Zingiber zerumbet*
[91]	–	Analgesic activity with ↓abdominal constriction and ↓paw licking time in all models by ↓protein kinase C and ↓glutamatergic system	Acetic acid-induced abdominal constriction and capsaicin-, glutamate-, and PMA-induced paw licking tests	Rhizome	

TPA 12-O-Tetradecanoylphorbol-13-acetate, *MPO* myeloperoxidase, *CFA* complete Freund's adjuvant, *IL-6* interleukin-6, *PGE2* prostaglandin-E2, *IFN-γ* interferon- γ, *TNBS* 2,4,6-Trinitrobenzene sulfonic acid, *TNF-α* tumor necrosis factor-alpha, *NF-κB* nuclear factor κB, *NO* nitric oxide, *MDA* malondialdehyde, *COXI* cyclooxygenase-1, *iNOS* inducible NO synthase, *SOD* superoxide dismutase, *GPx* glutathione peroxidase, *PL-A2* phospholipase A2, *LT-B4* leukotriene-B4, *EPP* ethyl phenylpropiolate, *5-HT* 5-Hydroxytryptamine, *12-LOX* 12-Lipoxygenase, *PMA* phorbol 12-myristate 13-acetate, *GABA* gamma-aminobutyric acid, *BALB/c* inbred strain of mouse, *PMN* polymorphonuclear

($P < 0.05$). One-month intake of capsules containing *N. sativa* seeds oil in a placebo-controlled trial on 40 women with rheumatoid arthritis resulted in amelioration of disease activity score, number of swollen joints, and duration of morning stiffness significantly [79]. Two clinical studies evaluated the efficacy and safety of ginger capsules in patients with OA. In a 6-week randomized, double-blind, placebo-controlled, multicenter, parallel-group clinical trial in 261 patients with OA of knee joint, daily intake of ginger extract capsule exhibited alleviation of pain of knee joint on standing and pain of knee after walking 50 feet significantly ($P = 0.048$ and $P = 0.016$, respectively).Ginger capsules also reduced Western Ontario and McMaster Universities OA composite indexes [97]. In a randomized controlled, double-blind, double-dummy, crossover clinical trial on 60 patients with OA of the knee, daily intake of capsules containing ginger extract (170 mg/day) for 3 weeks showed that the efficacy of ginger group was better than placebo in terms of visual analogue scale of pain and the Lequesne index, significantly ($P < 0.00001$ and $P < 0.00005$, respectively). Although in the crossover study in terms of Siegel–Castellan test, there was no significant difference between ginger extract and placebo. Result obtained from this clinical study showed that the efficacy of ginger extract in all of the evaluation was lower than the standard drug ibuprofen [98].

Among the clinical trials, no severe adverse effects were observed and the herbal preparations were commonly safe in human. Considering low number of human studies and their different restrictions like low methodological quality, small volume of patients, and single-center study, the levels of evidence for current review are low. Further clinical trials with high methodological quality and greater number of patients are needed to achieve more conclusive results on the potential efficacy and safety of medicinal herbs and their phytochemical agents in the management of OA.

Various natural components from medicinal plants have been isolated including dicaffeoylquinic acids, surinamensinols and acoramol, allyl amino acid derivatives and allyl sulfides, allivictoside, glucosyl kaempferol, 12-ursene 2-diketone, boswellic acid derivatives, cinnamic derivative, guggulsterol, diarylheptanoids, pseudohypericin, amentoflavone, myrtucommulones, zerumbone, kaempferol derivatives, stigmasterol and β-sitosterol, P-hydroxy benzoic acid, 5-(hydroxymethyl) furfural, bis(5-formylfurfuryl) ether, daucosterol, α-D-fructofuranosides methyl, uracil and stachydrine, procyanidine, 2-methoxy-8,12-epoxy-germacra-1 7,11-trine-6-one, 2-methoxy-5-acetoxy-furanogermacr-1 en-6-one, myrrhone, sandaracopimaric acid, abietic acid, dehydroabietic acid, mansumbinone, furanodiene and furanodienone, hyperoside, isoquercitrin and hypericin, α-linolenic acid, masticadienonic acid, masticadienolic acid and morolic acid, zerumbone, 3-O-methyl

Table 4 Clinical studies of medicinal plants used for the treatment for OA

Plant	Preparations		Study design	Disease	No. of patients	Treatment duration	Result	References
	Treatment group	Control group						
Boswellia serrata	Oleo-gum resin in capsule	Placebo	Randomized double-blind placebo-controlled trial	Osteoarthritis of the knee	30	8 weeks	↓Knee pain, ↑knee flexion, ↑walking distance and ↓swelling frequency in the knee joint significantly compared with placebo group ($P < 0.001$)	[47]
Matricaria chamomilla	Aerial part in a polyherbal topical ointment	Placebo	Placebo-controlled double-blind crossover trial	Osteoarthritis of the knee	42 (30 women and 12 men)	6 weeks	↓Pain of knee joint in primary knee osteoarthritis patient and ↓severity of disease-associated pain in comparison with placebo ($P < 0.05$)	[74]
Nigella sativa	Seeds oil capsules	Placebo	A placebo-controlled study	Rheumatoid arthritis womenpatients	40	1 month	↓Disease activity score significantly, ↓number of swollen joints and improvement of the duration of morning stiffness ($P = 0.017$)	[79]
Zingiber officinale	Capsule of ginger extract twice daily	Placebo	Randomized, double-blind, placebo-controlled, multicenter, parallel-group study	Osteoarthritis of the knee	261	6 week	↓Pain of knee joint on standing in comparison with control group ($P = 0.048$), ↑response of treatment in the analysis of the secondary efficacy variables, ↓pain of knee after walking 50 feet ($P = 0.016$) and ↓Western Ontario and McMaster Universities OA composite index	[97]
Zingiber officinale	Capsule of ginger extract 170 mg/day	Ibuprofen	Randomized controlled, double-blind, double-dummy, crossover study	Osteoarthritis of the knee	60	3 weeks	Efficacy of the extract group was better than placebo in visual analogue scale of pain ($P < 0.00001$) and in the Lequesne index ($P < 0.00005$), in the crossover study, no significant difference between ginger extract and placebo (Siegel–Castellan test); moreover, in explorative tests of differences, ginger extract was better than placebo ($P < 0.05$)	[98]

kaempferol, kaempferol-3-O-(2, 4-di-O-acetyl-α-l-rhamnopyranoside) and kaempferol-3-O-(3,4-di-O-acetyl-α-l-rhamnopyranoside), and some other phenolic compounds. Tables 2 and 3 show these phytochemical agents in detail. These components can be considered as novel natural drugs that may prove useful in the management of OA. More research is needed to develop therapeutic agents with disease-modifying properties to treat OA Table 4.

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References

1. Brooks PM (2002) Impact of osteoarthritis on individuals and society: how much disability? Social consequences and health economic implications. Curr Opin Rheumatol 14(5):573–577
2. Goldring MB, Goldring SR (2007) Osteoarthritis. J Cell Physiol 213(3):626–634. doi:10.1002/jcp.21258
3. Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, Im HJ (2013) A current review of molecular mechanisms regarding osteoarthritis and pain. Gene 527(2):440–447. doi:10.1016/j.gene.2013.05.069
4. Wood AM, Brock TM, Heil K, Holmes R, Weusten A (2013) A review on the management of hip and knee osteoarthritis. Int J Chron Dis 2013
5. Spector TD (1993) Epidemiology of the rheumatic diseases. Curr Opin Rheumatol 5(2):132–137
6. Hunter DJ, McDougall JJ, Keefe FJ (2008) The symptoms of osteoarthritis and the genesis of pain. Rheum Dis Clin North Am 34(3):623–643. doi:10.1016/j.rdc.2008.05.004
7. Sellam J, Berenbaum F (2010) The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol 6(11):625–635. doi:10.1038/nrrheum.2010.159
8. Houard X, Goldring MB, Berenbaum F (2013) Homeostatic mechanisms in articular cartilage and role of inflammation in osteoarthritis. Curr Rheumatol Rep 15(11):375. doi:10.1007/s11926-013-0375-6
9. Gardner GC (2005) Inflammatory arthritis in the era of the biologics. Clinical and Applied Immunology Reviews 5(1):19–44
10. Goldring MB, Otero M (2011) Inflammation in osteoarthritis. Curr Opin Rheumatol 23(5):471–478. doi:10.1097/BOR.0b013e328349c2b1
11. Fernandes JC, Martel-Pelletier J, Pelletier JP (2002) The role of cytokines in osteoarthritis pathophysiology. Biorheology 39(1–2):237–246
12. Roughley PJ (2006) The structure and function of cartilage proteoglycans. Eur Cells Mater 12:92–101
13. Huang K, Wu LD (2008) Aggrecanase and aggrecan degradation in osteoarthritis: a review. J Int Med Res 36(6):1149–1160
14. Sachs D, Cunha FQ, Poole S, Ferreira SH (2002) Tumour necrosis factor-alpha, interleukin-1beta and interleukin-8 induce persistent mechanical nociceptor hypersensitivity. Pain 96(1–2):89–97
15. Rezvanfar MA, Shojaei Saadi HA, Gooshe M, Abdolghaffari AH, Baeeri M, Abdollahi M (2014) Ovarian aging-like phenotype in the hyperandrogenism-induced murine model of polycystic ovary. Oxid Med Cell Longev 2014:10. doi:10.1155/2014/948951
16. Ziskoven C, Jager M, Kircher J, Patzer T, Bloch W, Brixius K, Krauspe R (2011) Physiology and pathophysiology of nitrosative and oxidative stress in osteoarthritic joint destruction. Can J Physiol Pharmacol 89(7):455–466. doi:10.1139/y11-055
17. Ziskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R (2010) Oxidative stress in secondary osteoarthritis: from cartilage destruction to clinical presentation? Orthop Rev (Pavia) 23(2):e23. doi:10.4081/or.2010.e23
18. Dieppe PA, Lohmander LS (2005) Pathogenesis and management of pain in osteoarthritis. Lancet 365(9463):965–973. doi:10.1016/s0140-6736(05)71086-2
19. Lee YC, Nassikas NJ, Clauw DJ (2011) The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther 13(2):211. doi:10.1186/ar3306
20. Felson DT (2005) The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 17(5):624–628
21. Lee AS, Ellman MB, Yan D, Kroin JS, Cole BJ, van Wijnen AJ, Im H-J (2013) A current review of molecular mechanisms regarding osteoarthritis and pain. Gene 527(2):440–447
22. van Laar M, Pergolizzi JV Jr, Mellinghoff HU, Merchante IM, Nalamachu S, O'Brien J, Perrot S, Raffa RB (2012) Pain treatment in arthritis-related pain: beyond NSAIDs. Open Rheumatol J 6:320–330. doi:10.2174/1874312901206010320
23. Dray A, Read SJ (2007) Arthritis and pain. Future targets to control osteoarthritis pain. Arthritis Res Ther 9(3):212. doi:10.1186/ar2178
24. Valdes AM, Spector TD (2011) Genetic epidemiology of hip and knee osteoarthritis. Nat Rev Rheumatol 7(1):23–32. doi:10.1038/nrrheum.2010.191
25. Kosek E, Ordeberg G (2000) Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 88(1):69–78
26. Long L, Soeken K, Ernst E (2001) Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology (Oxford, England) 40(7):779–793
27. Farzaei MH, Khanavi M, Moghaddam G, Dolatshahi F, Rahimi R, Shams-Ardekani MR, Amin G, Hajimahmoodi M (2014) Standardization of Tragopogon graminifolius DC. extract based on phenolic compounds and antioxidant activity. J Chem 2014:6. doi:10.1155/2014/425965
28. Benedek B, Kopp B, Melzig MF (2007) Achillea millefolium L. s.l.—is the anti-inflammatory activity mediated by protease inhibition? J Ethnopharmacol 113(2):312–317. doi:10.1016/j.jep.2007.06.014
29. Zaringhalam J, Akbari A, Tekieh E, Manaheji H, Rezazadeh S (2010) Achillea santolina reduces serum interleukin-6 level and hyperalgesia during complete Freund's adjuvant-induced inflammation in male Wistar rats. J Chin Integr Med 8(12):1180–1189
30. Gomez M, Saenz M, Garcia M, Fernandez M (1999) Study of the topical anti-inflammatory activity of Achillea ageratum on chronic and acute inflammation models. Z Naturforsch C 54(12):937–941
31. Elmann A, Mordechay S, Erlank H, Telerman A, Rindner M, Ofir R (2011) Anti-Neuroinflammatory effects of the extract of Achillea fragrantissima. BMC Complement Altern Med 11(1):98
32. Kim H, Han TH, Lee SG (2009) Anti-inflammatory activity of a water extract of Acorus calamus L. leaves on keratinocyte HaCaT cells. J Ethnopharmacol 122(1):149–156. doi:10.1016/j.jep.2008.12.011
33. Khan MAA, Islam MT (2012) Analgesic and cytotoxic activity of Acorus calamus L., Kigelia pinnata L., Mangifera indica L. and Tabernaemontana divaricata L. J Pharm Bioallied Sci 4(2):149
34. Hodge G, Hodge S, Han P (2002) Allium sativum (garlic) suppresses leukocyte inflammatory cytokine production in vitro: potential therapeutic use in the treatment of inflammatory bowel disease. Cytometry 48(4):209–215
35. Simin N, Orcic D, Cetojevic-Simin D, Mimica-Dukic N, Anackov G, Beara I, Mitic-Culafic D, Bozin B (2013) Phenolic

profile, antioxidant, anti-inflammatory and cytotoxic activities of small yellow onion (*Allium flavum* L. subsp. *flavum*, Alliaceae). LWT-Food Science and Technology
36. Woo KW, Moon E, Park SY, Kim SY, Lee KR (2012) Flavonoid glycosides from the leaves of Allium victorialis var. platyphyllum and their anti-neuroinflammatory effects. Bioorg Med Chem Lett 15(24):7465–7470. doi:10.1016/j.bmcl
37. Habeeb F, Stables G, Bradbury F, Nong S, Cameron P, Plevin R, Ferro VA (2007) The inner gel component of Aloe vera suppresses bacterial-induced pro-inflammatory cytokines from human immune cells. Methods 42(4):388–393
38. Kammoun M, Miladi S, Ben Ali Y, Damak M, Gargouri Y, Bezzine S (2011) In vitro study of the PLA2 inhibition and antioxidant activities of Aloe vera leaf skin extracts. Lipids Health Dis 10:30. doi:10.1186/1476-511x-10-30
39. Vijayalakshmi D, Dhandapani R, Jayaveni S, Jithendra PS, Rose C, Mandal AB (2012) In vitro anti inflammatory activity of Aloe vera by down regulation of MMP-9 in peripheral blood mononuclear cells. J Ethnopharmacol 141(1):542–546
40. Davis RH, Rosenthal KY, Cesario LR, Rouw GA (1989) Processed Aloe vera administered topically inhibits inflammation. J Am Podiatr Med Assoc 79(8):395–397
41. Hage-Sleiman R, Mroueh M, Daher CF (2011) Pharmacological evaluation of aqueous extract of Althaea officinalis flower grown in Lebanon. Pharm Biol 49(3):327–333. doi:10.3109/13880209.2010.516754
42. Wang D, Shang J, Yu Q (1989) Analgesic and anti-inflammatory effects of the flower of Althaea rosea (L.) Cav]. China J Chin Mater Med 14(1):46
43. Kim YJ, Shin Y, Lee KH, Kim TJ (2012) Anethum graveloens flower extracts inhibited a lipopolysaccharide-induced inflammatory response by blocking iNOS expression and NF-kappaB activity in macrophages. Biosci Biotechnol Biochem 76(6):1122–1127
44. Valadi A, Nasri S, Abbasi N, Amin GR (2010) ANTInociceptive and anti-inflammatory effects of hydroalchoholic extract of anethum graveolens L. Seed. J Med Plants 9(34):124–130
45. Fan AY, Lao L, Zhang RX, Zhou AN, Wang LB, Moudgil KD, Lee DY, Ma ZZ, Zhang WY, Berman BM (2005) Effects of an acetone extract of Boswellia carterii Birdw. (Burseraceae) gum resin on adjuvant-induced arthritis in lewis rats. J Ethnopharmacol 101(1–3):104–109. doi:10.1016/j.jep.2005.03.033
46. Gayathri B, Manjula N, Vinaykumar KS, Lakshmi BS, Balakrishnan A (2007) Pure compound from Boswellia serrata extract exhibits anti-inflammatory property in human PBMCs and mouse macrophages through inhibition of TNFalpha, IL-1beta, NO and MAP kinases. Int Immunopharmacol 7(4):473–482. doi:10.1016/j.intimp.2006.12.003
47. Kimmatkar N, Thawani V, Hingorani L, Khiyani R (2003) Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee—a randomized double blind placebo controlled trial. Phytomedicine 10(1):3–7. doi:10.1078/094471103321648593
48. Danquah CA, Woode E, Boakye-Gyasi E (2011) Anti-arthritic effects of an ethanolic extract of capparis erythrocarpos isert roots in Freund's adjuvant-induced arthritis in rats. J Pharmacol Toxicol 6(3):201–217
49. Feng X, Lu J, Xin H, Zhang L, Wang Y, Tang K (2011) Anti-arthritic active fraction of Capparis spinosa L. fruits and its chemical constituents. Yakugaku Zasshi 131(3):423–429
50. Bektas N, Arslan R, Goger F, Kirimer N, Ozturk Y (2012) Investigation for anti-inflammatory and anti-thrombotic activities of methanol extract of *Capparis ovata* buds and fruits. J Ethnopharmacol 142(1):48–52
51. Arslan R, Bektas N, Ozturk Y (2010) Antinociceptive activity of methanol extract of fruits of *Capparis ovata* in mice. J Ethnopharmacol 131(1):28–32
52. Lewis A, Levy A (2011) Anti-inflammatory activities of Cassia alata leaf extract in complete Freund's adjuvant arthritis in rats. West Indian Med J 60(6):615–621
53. Sreejith G, Latha P, Shine V, Anuja G, Suja S, Sini S, Shyamal S, Pradeep S, Shikha P, Rajasekharan S (2010) Anti-allergic, anti-inflammatory and anti-lipidperoxidant effects of Cassia occidentalis Linn
54. Nsonde Ntandou G, Banzouzi J, Mbatchi B, Elion-Itou R, Etou-Ossibi A, Ramos S, Benoit-Vical F, Abena A, Ouamba J (2010) Analgesic and anti-inflammatory effects of *Cassia siamea* Lam. stem bark extracts. J Ethnopharmacol 127(1):108–111
55. Liao JC, Deng JS, Chiu CS, Hou WC, Huang SS, Shie PH, Huang GJ (2012) Anti-inflammatory activities of cinnamomum cassia constituents in vitro and in vivo. Evid Based Complement Alternat Med: eCAM 2012:429320. doi:10.1155/2012/429320
56. Yu T, Lee S, Yang WS, Jang HJ, Lee YJ, Kim TW, Kim SY, Lee J, Cho JY (2012) The ability of an ethanol extract of Cinnamomum cassia to inhibit Src and spleen tyrosine kinase activity contributes to its anti-inflammatory action. J Ethnopharmacol 139(2):566–573. doi:10.1016/j.jep.2011.11.051
57. Vetal S, Bodhankar SL, Mohan V, Thakurdesai PA (2013) Anti-inflammatory and anti-arthritic activity of type-A procyanidine polyphenols from bark of *Cinnamomum zeylanicum* in rats. Food Sci Human Wellness
58. Nair V, Kumar R, Singh S, Gupta Y (2012) Investigation into the anti-inflammatory and antigranuloma activity of Colchicum luteum Baker in experimental models. Inflammation 35(3):881–888
59. Nair V, Singh S, Gupta Y (2011) Evaluation of the disease modifying activity of *Colchicum luteum* Baker in experimental arthritis. J Ethnopharmacol 133(2):303–307
60. Su S, Wang T, Duan J-A, Zhou W, Hua Y-Q, Tang Y-P, Yu L, Qian D-W (2011) Anti-inflammatory and analgesic activity of different extracts of Commiphora myrrha. J Ethnopharmacol 134(2):251–258
61. Manjula N, Gayathri B, Vinaykumar KS, Shankernarayanan NP, Vishwakarma RA, Balakrishnan A (2006) Inhibition of MAP kinases by crude extract and pure compound isolated from Commiphora mukul leads to down regulation of TNF-alpha, IL-1beta and IL-2. Int Immunopharmacol 6(2):122–132. doi:10.1016/j.intimp.2005.07.001
62. Makabe H, Maru N, Kuwabara A, Kamo T, Hirota M (2006) Anti-inflammatory sesquiterpenes from Curcuma zedoaria. Nat Prod Res 20(7):680–685
63. Kaushik ML, Jalalpure SS (2011) Effect of Curcuma zedoaria Rosc root extracts on behavioral and radiology changes in arthritic rats. J Adv Pharm Technol Res 2(3):170
64. Sodsai A, Piyachaturawat P, Sophasan S, Suksamrarn A, Vongsakul M (2007) Suppression by Curcuma comosa Roxb. of pro-inflammatory cytokine secretion in phorbol-12-myristate-13-acetate stimulated human mononuclear cells. Int Immunopharmacol 7(4):524–531. doi:10.1016/j.intimp.2006.12.013
65. Ahmadiani A, Hosseiny J, Semnanian S, Javan M, Saeedi F, Kamalinejad M, Saremi S (2000) Antinociceptive and anti-inflammatory effects of Elaeagnus angustifolia fruit extract. J Ethnopharmacol 72(1):287–292
66. Liao C-R, Chang Y-S, Peng W-H, Lai S-C, Ho Y-L (2012) Analgesic and anti-inflammatory activities of the methanol extract of Elaeagnus oldhamii Maxim. in mice. Am J Chin Med 40(03):581–597
67. Huang N, Rizshsky L, Hauck CC, Nikolau BJ, Murphy PA, Birt DF (2012) The inhibition of lipopolysaccharide-induced macrophage inflammation by 4 compounds in *Hypericum perforatum* extract is partially dependent on the activation of SOCS3. Phytochemistry 76:106–116
68. Hammer KD, Yum M-Y, Dixon PM, Birt DF (2010) Identification of JAK–STAT pathways as important for the anti-inflammatory

activity of a *Hypericum perforatum* fraction and bioactive constituents in RAW 264.7 mouse macrophages. Phytochemistry 71(7):716–725
69. Süntar IP, Akkol EK, Yılmazer D, Baykal T, Kırmızıbekmez H, Alper M, Yeşilada E (2010) Investigations on the in vivo wound healing potential of hypericum perforatum L. J Ethnopharmacol 127(2):468–477
70. Sanchez-Mateo CC, Bonkanka CX, Hernandez-Perez M, Rabanal RM (2006) Evaluation of the analgesic and topical anti-inflammatory effects of Hypericum reflexum L. fil. J Ethnopharmacol 107(1):1–6. doi:10.1016/j.jep.2006.01.032
71. Kaithwas G, Majumdar DK (2010) Therapeutic effect of Linum usitatissimum (flaxseed/linseed) fixed oil on acute and chronic arthritic models in albino rats. Inflammopharmacology 18(3):127–136
72. Kaithwas G, Mukherjee A, Chaurasia A, Majumdar DK (2011) Antiinflammatory, analgesic and antipyretic activities of Linum usitatissimum L.(flaxseed/linseed) fixed oil
73. Abad A, Nouri M, Gharjanie A, Tavakoli F (2011) Effect of *Matricaria chamomilla* Hydroalcoholic extract on cisplatin-induced neuropathy in mice. Chin J Nat Med 9(2):126–131
74. Soltanian AR, Mehdibarzi D, Faghihzadeh S, Naseri M, Gerami A (2010) Mixture of Arnebia euchroma and Matricaria chamomilla (Marhame-Mafasel) for pain relief of osteoarthritis of the knee–a two-treatment, two-period crossover trial. Archives Med Sci: AMS 6(6):950
75. Feisst C, Franke L, Appendino G, Werz O (2005) Identification of molecular targets of the oligomeric nonprenylated acylphloroglucinols from Myrtus communis and their implication as anti-inflammatory compounds. J Pharmacol Exp Ther 315(1):389–396
76. Maxia A, Frau MA, Falconieri D, Karchuli MS, Kasture S (2011) Essential oil of Myrtus communis inhibits inflammation in rats by reducing serum IL-6 and TNF-alpha. Nat Prod Commun 6(10):1545–1548
77. Hosseinzadeh H, Khoshdel M, Ghorbani M (2011) Antinociceptive, Anti-inflammatory Effects and Acute Toxicity of Aqueous and Ethanolic Extracts of *Myrtus communis* L. aerial parts in mice. J Acupunct Meridian Stud 4(4):242–247
78. Ghannadi A, Hajhashemi V, Jafarabadi H (2005) An investigation of the analgesic and anti-inflammatory effects of Nigella sativa seed polyphenols. J Med Food 8(4):488–493
79. Gheita TA, Kenawy SA (2012) Effectiveness of Nigella sativa oil in the management of rheumatoid arthritis patients: a placebo controlled study. Phytother Res 26(8):1246–1248
80. Dang G, Parekar R, Kamat S, Scindia A, Rege N (2011) Antiinflammatory activity of Phyllanthus emblica, Plumbago zeylanica and Cyperus rotundus in acute models of inflammation. Phytother Res 25(6):904–908
81. Kiemer AK, Hartung T, Huber C, Vollmar AM (2003) *Phyllanthus amarus* has anti-inflammatory potential by inhibition of iNOS, COX-2, and cytokines via the NF-κB pathway. J Hepatol 38(3):289–297
82. Kassuya CA, Silvestre AA, Rehder VLG, Calixto JB (2003) Anti-allodynic and anti-oedematogenic properties of the extract and lignans from *Phyllanthus amarus* in models of persistent inflammatory and neuropathic pain. Eur J Pharmacol 478(2):145–153
83. Ahmad NS, Waheed A, Farman M, Qayyum A (2010) Analgesic and anti-inflammatory effects of *Pistacia integerrima* extracts in mice. J Ethnopharmacol 129(2):250–253
84. Maxia A, Sanna C, Frau MA, Piras A, Karchuli MS, Kasture V (2011) Anti-inflammatory activity of Pistacia lentiscus essential oil: involvement of IL-6 and TNF-alpha. Nat Prod Commun 6(10):1543–1544
85. Giner-Larza EM, Manez S, Giner RM, Recio MC, Prieto JM, Cerdá-Nicolás M, Ríos J (2002) Anti-inflammatory triterpenes from Pistacia terebinthus galls. Planta Med 68(04):311–315
86. Raghav S, Gupta B, Agrawal C, Goswami K, Das H (2006) Anti-inflammatory effect of *Ruta graveolens* L. in murine macrophage cells. J Ethnopharmacol 104(1):234–239
87. Ratheesh M, Shyni G, Helen A (2009) Methanolic extract of Ruta graveolens L. inhibits inflammation and oxidative stress in adjuvant induced model of arthritis in rats. Inflammopharmacology 17(2):100–105
88. Ratheesh M, Shyni G, Sindhu G, Helen A (2010) Protective effects of isolated polyphenolic and alkaloid fractions of Ruta graveolens L. on acute and chronic models of inflammation. Inflammation 33(1):18–24
89. Ahmadiani A, Fereidoni M, Semnanian S, Kamalinejad M, Saremi S (1998) Antinociceptive and anti-inflammatory effects of *Sambucus ebulus* rhizome extract in rats. J Ethnopharmacol 61(3):229–235
90. Chien T, Chen L, Lee C, Lee F, Wang C (2008) Anti-inflammatory constituents of Zingiber zerumbet. Food Chem 110(3):584–589
91. Khalid MH, Akhtar MN, Mohamad AS, Perimal EK, Akira A, Israf DA, Lajis N, Sulaiman MR (2011) Antinociceptive effect of the essential oil of *Zingiber zerumbet* in mice: possible mechanisms. J Ethnopharmacol 137(1):345–351
92. Shen CL, Smith BJ, Lo DF, Chyu MC, Dunn DM, Chen CH, Kwun IS (2012) Dietary polyphenols and mechanisms of osteoarthritis. J Nutr Biochem 23(11):1367–1377. doi:10.1016/j.jnutbio.2012.04.001
93. Kim KH, Moon E, Kim HK, Oh JY, Kim SY, Choi SU, Lee KR (2012) Phenolic constituents from the rhizomes of Acorus gramineus and their biological evaluation on antitumor and anti-inflammatory activities. Bioorg Med Chem Lett 22(19):6155–6159. doi:10.1016/j.bmcl.2012.08.016
94. Gomez MA, Saenz MT, Garcia MD, Fernandez MA (1999) Study of the topical anti-inflammatory activity of Achillea ageratum on chronic and acute inflammation models. Z Naturforsch [C] 54(11):937–941
95. Mohammadi-Motlagh H-R, Mostafaie A, Mansouri K (2011) Anticancer and anti-inflammatory activities of shallot
96. Ramezani M, Hosseinzadeh H, Daneshmand N (2001) Antinociceptive effect of Elaeagnus angustifolia fruit seeds in mice. Fitoterapia 72(3):255–262
97. Altman RD, Marcussen KC (2001) Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum 44(11):2531–2538
98. Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, Christensen K, Jensen ON, Barslev J (2000) A randomized, placebo-controlled, cross-over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthr Cartil/OARS, Osteoarthr Res Soc 8(1):9–12. doi:10.1053/joca.1999.0264