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Review

A mechanistic review on medicinal plants used for rheumatoid arthritis in traditional Persian medicine

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Abstract

Objectives Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, which affects synovial tissue in multiple joints. Although conventional treatments of RA commonly alleviate the symptoms, high incidence of adverse reactions leads to research tendency towards complementary and alternative medicine. As various medicinal plants are traditionally used for the management of symptomatologies associated with RA in Persian medicine, we reviewed medicinal literature to confirm their efficacy in the management of RA.

Key findings Scientific evidence revealed that traditional medicaments exert beneficial effects on RA through several cellular mechanisms including downregulation of pro-inflammatory cytokines such as TNF-α, IL-6 and NF-κB, suppression of oxidative stress, inhibition of cartilage degradation with destructive metalloproteinases and enhancement of antioxidant performance. Various active constituents from different chemical categories including flavonols, lignans, coumarins, terpenes, glycosylflavons, dihydroflavonols, phytoestrogens, sesquiterpene lactones, anthraquinones, alkaloids and thymoquinones have been isolated from the medicinal plants.

Summary The pharmacological mechanisms of the medicinal plants traditionally used for RA in Persian medicine are discussed in the current review. Further investigations are mandatory to focus on bioefficacy of these phytochemicals for finding novel natural drugs.

Introduction

Inflammatory processes play a pivotal role in the development of various diseases. Chronic inflammation arises in pathologic conditions including exposure to toxic agents, resistant infections caused by certain microorganisms as well as autoimmunity. Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease, which affects synovial tissue in multiple joints and is characterized by joint swelling, cartilage damage, synovial inflammation and bony erosion, which can finally result in joint destruction.[1–3] The total world prevalence of RA is about 0.5–1% and is three to four times more common in women.[2] The initiation of RA is unknown, although interactions between genetic factors, sex hormones and an immune triggering agent (endogen or environmental substances which triggers an immune response) are considered as contributing factors.[2,4]

In RA, synoviocytes and macrophages produce joint-damaging cytokines. These pro-inflammatory cytokines inhibit the synthesis of proteoglycans and collagen and increase their degradation. They also activate proteolytic enzymes (i.e. MMPs and collagenases) promoting destruction of cartilage.[3–5] Pro-inflammatory cytokines, such as interleukin-1β (IL-1β), IL-6 and tumour necrosis factor-α (TNF-α), stimulate articular manifestations of RA through increasing inflammatory cell infiltration, particularly T

cells, B cells, and macrophages, and bone erosion. T-cell activation results in autoantibody production and release of TNF-α and IL-6; in consequence, the articular and extra-articular manifestation of RA occurs. Chemotactic cytokines, termed chemokines which attract lymphocytes, monocytes and neutrophils, possess chemotactic activity and play a significant role in tissue destruction and synovitis. The pro-inflammatory enzyme, cyclooxygenase (COX)-2, converts arachidonic acid into prostaglandin-E2 (PGE2) and prompts hyperplasia and pannus formation in synovial joints resulting in suppression of apoptosis in synovial fibroblasts and induction of proliferation. Regulation of arachidonic acid metabolism and modulation of other mediators secreted by macrophages and other immune cells can be potential targets for the treatment of chronic inflammatory conditions by inhibiting enzymes like COX and lipooxygenase (LOX).[3,5–7]

The goal of conventional treatment is to slow or reverse cartilage degradation and decrease the pain without toxic pharmacological consequences. Disease-modifying anti-rheumatic drugs (DMARDs) and biological agents including anti-TNF-α are used for the prevention of swelling, pain and joint destruction in RA. Nevertheless, current treatment with DMARDs is not effective in all patients. Immunosuppressants, nonsteroidal anti-inflammatory drugs (NSAIDs) and steroidal anti-inflammatory drugs are commonly used for alleviation of RA complication, but potential side effects limit their use. For example, NSAIDs and steroids can cause adverse haematologic, gastrointestinal and renal complications. Long-term administration of these drugs may lead to adverse effects such as increased risk of gastrointestinal ulceration and bleeding due to suppression of COX-l. Therefore, many patients look for complementary and alternative medicine (CAM) approaches for the management of debilitating diseases with chronic pain, such as RA.[3,8,9]

Traditional medicines all over the world suggest a wide range of remedies for the management of symptomatologies associated with chronic disorders as in RA. Scientists are exploring within nations' traditional medicine to find alternative anti-arthritic drugs. Medicinal plants and plant-derived natural agents are among the most important resources of traditional medicines.[10–13] Traditional Persian medicine dates back to thousands of years. History of medicine in Iran was initiated almost in the fourth century BC.[14,15] It is suggested that traditional Persian medicine has played a key role in historical progress of pharmaceutical sciences.[16–19]

In traditional Persian literature, the term rheumatoid arthritis is expressed as a disturbance in humoral balance of the body, which commonly occurs in subjects with 'cold' and 'moist' temperaments. Patients with this humoral disorder suffer from chronic pain in the joints '*waja'-e-mafasel*', mainly due to accumulation of phlegm in the joints.[20,21]

To our knowledge, there is no mechanistic and evidence-based review on traditional medicinal plants used for RA in Persian medicine. As various medicinal plants have traditionally been used for RA managements in Persian medicine, we reviewed medicinal literature to confirm their efficacy and safety in the management of RA. In addition, molecular and biological mechanisms of action along with active phytochemical agents were highlighted, in favour of plating future drugs for the treatment of RA.

Method

In the current study, a list of medicinal plants traditionally used topically or orally for the treatment of RA was collected from traditional Persian literature, including Al-Qanoon fi al-Tibb (The Canon of Medicine, written by Avicenna in 1025 CE),[20] Makhzan-ol-advieh (written by Aghili Alavi Khorasani in 1771 CE),[22] Qarabadin-e-kabir (the largest pharmaceutical manuscript of Persian medicine, written by Aghili Alavi Khorasani in 1772 CE)[22] and Tohfat-ol-Moemenin (written by Mohammad Tonkaboni in 1670 CE).[23] Subsequently, electronic databases including Scirus, PubMed, Scopus, Web of Science, Google Scholar and Cochrane library were explored for each of these plants, and all retrieved articles were evaluated to ascertain any *in vitro*, *in vivo* or clinical evidence for their efficacy and pharmacological mechanisms. The retrieved studies demonstrated either apparent efficiency of these remedies or their indirect effectiveness on the mechanisms involved in the management of RA. Data were collected from 1970 to 2014 (December). Only published articles were included in this review. Language restriction was considered, and English language articles were included. The search terms were 'rheumatoid arthritis' or 'arthritis' or 'inflammation' and the name of each mentioned plant in the whole text. Results from primary search were screened by two independent investigators. References of finally included articles were reviewed for relevant studies. Included articles were reviewed to extract scientific names of plants, part and extract of the plants, active components (if mentioned), type of inflammation or arthritis, animal model for *in vivo* and type of cell line for in vitro studies. Results were considered to determine differences between test groups and control groups in terms of pro-inflammatory cytokines, joint swelling, cartilage degradation, tissue oedema, granuloma formation, inflammatory reactions, leucocyte infiltration, number of inflammatory cells, antioxidant enzymes and factors, disease activity index and proteolytic enzymes. Results are summarized in Tables 1, 2, 3 and 4. Table 1 demonstrates the selected medicinal plants used for the treatment of RA in traditional Persian medicine. Tables 2, 3 and 4 show *in vitro*, *in vivo* and clinical evidence for the efficacy of the medicinal plants in rheumatoid disorders. In

Table 1 Medicinal plants traditionally used for the treatment of RA in traditional Persian medicine

Scientific names	Family	Vernacular name(s)	Traditional uses [20,22,23]
Alhagi camelorum Fisch.	Fabaceae	*Khar-e-shotor (resin)*	Diuretic, antinociceptive, joint pain and RA
Althaea officinalis L.	Malvaceae	*Khatmi (flower)*	Respiratory disorders, peptic ulcer, colitis, inflammation, antinociceptive, joint pain and RA
Arctium lappa L.	Asteraceae	Arghitun	Fissure, burn wound, joint pain and RA
Artemisia absinthium L.	Asteraceae	Afsantin (aerial part)	Gastric tonic, neuralgia, diuretic, inflammation, joint paint and RA
Astragalus arbusculinus Bornm. & Gauba	Fabaceae	Anzarut (gum)	Antinociceptive, joint pain and arthritis
Cassia angustifolia M. Vahl	Fabaceae	Sanaa (leaf)	Laxative, migraine, purgative of phlegm, RA
Citrus medica L.	Rutaceae	Otroj, Toranj (fruit)	Inflammation, goat, antidepressant, headache, joint pain and RA
Clematis ochroleuca Aiton	Ranunculaceae	Zeyan, Yasamin-e-zard	Respiratory disorders, headache, joint pain and RA
Colchicum autumnale L.	Colchicaceae	Surenjan, Golhasrat (corm)	Inflammation, goat, haemorrhoid, hepatitis, joint pain and RA
Convolvulus arvensis L.	Convolvulaceae	Lablab-e-saghir	Inflammation, respiratory disorders, joint pain and RA
Cuscuta epithymum L.	Convolvulaceae	Aftimun, Sos-e-shabdari (fruit)	Headache, joint pain and RA
Dolichos lablab L.	Fabaceae	Lablab-e-kabir	Headache, inflammation, diuretic, wound, joint pain and RA
Dorema ammoniacum D. Don.	Apiaceae	Oshagh, Vasha (rhizome)	Diuretic, antinociceptive, respiratory disorders, hepatitis, joint pain and RA
Ferula assa-foetida L.	Apiaceae	Anjedan, Anghuze (oleo-gum resin)	Gastric tonic, appetizer, hepatitis, diuretic, joint pain and RA
Ferula persica L.	Apiaceae	Sakbinaj (oleo-gum resin)	Goat, headache, haemorrhoid, joint pain and RA
Inula helenium L.	Asteraceae	Rasan, Zanjabil-e-shami	Antidepressant, inflammation, liver disorder, diuretic, joint pain and RA
Narcissus tazzeta L.	Amaryllidaceae	Narges	Wound healing, goat, antinociceptive, joint pain and RA
Nepeta menthoides Boiss. & Buhse	Lamiaceae	Ostokhodus (aerial part)	Gastric tonic, inflammation, antidepressant, haemorrhoid, joint pain and RA
Nigella sativa L.	Ranunculaceae	*Shuniz, Siah dane (seed)*	Diuretic, hepatitis, headache, haemorrhoid, joint pain and RA
Opopanax chironium W.D.J.Koch	Apiaceae	Javshir	Antinociceptive, diuretic, goat, headache, joint pain and RA
Peganum harmala L.	Nitrariaceae	Harmal, esfand	Diuretic, headache, liver disorder, antinociceptive, joint pain and RA
Rheum palmatum L.	Polygonaceae	Rivand-e-chini	Diuretic, haemorrhoid, Respiratory disorders, joint pain and RA
Smilax china L. and *S. glabra* Roxb.	Smilacaceae	Ashabe-ye- maghrebi	Inflammation, gastric tonic, goat, haemorrhoid, diuretic, joint pain and RA
Strychnos nux-vomica L.	Loganiaceae	Azaraghi, Marg-e-moosh	Joint pain and RA

human studies, factors such as study design, number of patients, interventions, duration of treatment and efficacy and tolerability of the herbal treatment were also collected.

Finding and Results

Scientific and vernacular names of medicinal plants used for the treatment of RA in traditional Persian literature are shown in Table 1. Moreover, details of *in vitro* and *in vivo* findings that support their efficacy in RA are demonstrated in Tables 2 and 3. Table 4 shows clinical trials on mentioned medicinal plants. Below, these medicinal plants with their possible mechanisms of action along with active phytochemical agents in the management of RA are described.

Althaea officinalis L. (Malvaceae)

The flowers of *A. officinalis*, commonly known as marshmallow, have traditionally been used for the treatment of inflammatory diseases and chronic pain from the ancient time. In traditional Persian medicine, this remedy possesses a wide range of therapeutic indications such as respiratory disorders, colitis and joint pains. The flowers of *A. officinalis* possess anti-inflammatory activity and decrease capillaries permeability by attenuating release of PGE from inflammatory tissue.[24,25]

Scopoletin, one of the main constituent of the leaves of *A. officinalis*, can improve RA through inhibiting the release of the pro-inflammatory cytokines PGE2, TNF-α, IL-1β and IL-6 and suppressing the expression of COX-2.[26,27] Scientific literature suggests activation of a transcription factor, namely nuclear factor (NF), which binds to significant consensus DNA factors that exist on the promoter of specific genes, to trigger the expression of pro-inflammatory cytokines. Scopoletin significantly downregulates *Rel* A (p65) that is a subfamily of NF-κB in nucleus of human mast cell line. It is reported that activation of NF-κB is mediated by phosphorylation and degradation of

Table 2 In vitro studies on medicinal plants traditionally used for the treatment of RA

Plant	Part/extraction	Result	Active constituent	References
Arctium lappa	Seeds/Ethanolic extract	Anti-inflammatory activity via ↓NO, ↓iNOS, ↓TNF-α and ↓IL-6 on LPS-induced RAW 264.7 macrophage	Arctigenin	[33]
	Root/Butanolic extract	Anti-inflammatory activity via ↓IL-4, ↓IL-5, ↓NF-κB and ↓MAPKs phosphorylation on Con A-induced primary splenocytes	–	[34]
	Seeds/-	Arctigenin showed anti-inflammatory activity by ↓IL-1β, ↓IL-6 and ↓TNF-α on PGN- and LPS-induced peritoneal macrophages	Arctigenin and glycoside arctiin	[35]
Artemisia capillaris	Shoot/Hot water extract	Anti-inflammatory activity via ↓NO, ↓PGE2, ↓iNOS, ↓COX-2, ↓TNF-α, ↓IL-1β and ↓IL-6 on IFN-γ- and LPS-stimulated RAW 264.7 macrophages	Scoparone	[37]
Artemisia sylvatica	Aerial parts/Methanol extract	Anti-inflammatory activity by ↓NF-κB, ↓NO, ↓TNF-α, ↓COX-2 and ↓iNOS on LPS-induced RAW264.7 macrophages	Artemisolide, 3-methoxytanapartholide, deacetyllaurenobiolide, moxartenolide as well as arteminolides B and D	[40]
Citrus medica	Peel/Ethanol extract	Anti-inflammatory activity by ↓NO, ↓TNF-α, ↓PGE2, ↓iNOS, ↓COX-2, ↓NF-κB, ↓IL-1β,↓IL-6, ↓JNK and ↓ERK on LPS-stimulated mouse RAW 264.7 macrophages	Limonene and γ-terpinene	[45]
Clematis chinensis	Root/Acetone extract	Anti-inflammatory activity via ↓PGE2, ↓MMP-3 and ↓COX-2 on IL-1β-and LPS-stimulated PHC	Saponins	[48]
Clematis mandshurica	Root/Ethanolic extract	Anti-inflammatory activity by↓PGE2 and ↓NO on LPS- and IFN γ-stimulated mouse peritoneal macrophages as well as ↓IL-2 and ↓IFN-γ on Con A-activated splenocytes	–	[47]
Cuscuta campestris	Seeds/Ethanolic extract	Anti-inflammatory activity by ↓NO on LPS-induced murine RAW264.7 macrophages	Quercetin	[55]
Cuscuta reflexa	Seeds/Ethanolic extract	Anti-inflammatory activity by ↓TNF-α, ↓COX-2 and ↓NF-κB on LPS-induced murine RAW264 macrophages	–	[56]
Inula falconeri	Aerial part/Ethanolic extract	Anti-inflammatory activity via ↓NO on LPS-induced RAW264.7 macrophages	Guaiane, pseudoguaiane, xanthane, eudesmane, germacrane, rare secocaryophyllane, chromolaevane and carabrane	[64]
Inula viscosa	Aerial part/Dichloromethanic extract	Anti-inflammatory activity via ↓5-LOX and ↓LT-B4 in peritoneal rat neutrophils	7-O-methylaromadendrin, 3-acetyl-7-O-methylaromadendrin and sakuranetin	[63]
Rheum palmatum L.	Root/-	Anti-inflammatory activity via ↓TNF-α, ↓IL-6 ,↓IL-8, ↓PGE2, ↓MMP-1, ↓COX-2 and ↓VEGF in IL-1β and LPS-stimulated synoviocytes	Emodin	[70]
Smilax china L.	Rhizome/Ethanolic extracts	Anti-inflammatory activity via ↓NO, ↓TNF-α and ↓NF-κB in LPS-induced murine macrophages	–	[72]
Smilax glabra	Rhizome/Aqueous extract	Anti-inflammatory activity via ↓IL-1 and ↓NO on LPS-induced peritoneal macrophages, as well as ↓T lymphocyte proliferation and ↓IL-2 production on Con A-induced splenocytes	–	[71]

NO, nitric oxide; IL, interleukin; TNF-α, tumour necrosis factor-alpha; COX-2, cyclooxygenase-2; iNOS, inducible NO synthase; LPS, lipopolysaccharide; NF-κB, nuclear factor κB; 5-LOX, 5-lipoxygenase; IFN-γ, interferon- γ; IgG, Immunoglobulin G; MAPKs, Mitogen-activated protein kinase; Con A, concanavalin A; CYP P450, cytochrome P450; PHC, Primary human chondrocytes; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase; LT-B4, leukotriene-B4; PGE2, prostaglandin-E2; Caco-2, colon adenocarcinoma-2; VEGF, vascular endothelial growth factor. ↑ and ↓ show increase and decrease in mentioned variables, respectively.

Table 3 In vivo studies on medicinal plants traditionally used for the treatment of RA

Plant	Part/extraction	Method/route of administration	Animal	Result	Active constituents	References
Althaea officinalis	Flower/Aqueous extract	Carrageenan- and formalin-induced oedema/Oral administration	Rat	↓Inflammation in both model	–	[25]
Althaea rosea	Flower/Ethanolic extract	Acetic acid-induced increase permeability of abdominal capillaries and carrageenan- and dextran-induced paw oedema/Oral administration	Rat	↓Permeability of abdominal capillaries, ↓paw oedema in all models by ↓release of PGE from inflammatory tissue	–	[24]
Arctium minus	Leaves/Ethanolic extract	Carrageenan-induced paw oedema/Oral administration	Mouse	Ethanolic extract showed ↓paw oedema	–	[36]
Artemisia capillaris	Aerial part/Ethanolic extract	Arachidonic acid-induced ear oedema/ Oral administration	Mouse	↓Ear oedema	Scopoletin, scopolin, scoparone, esculetin, quercetin, capillarisin, isorhamnetin, 3-O-robinobioside, isorhamnetin 3-O-galactoside and chlorogenic acid	[41]
Artemisia douglasiana	Aerial parts/Ethanol extract	CFA-induced oedema and cotton pellet-induced granuloma/Oral administration	Rat	↓Inflammation via ↓NF-κB and ↓granuloma formation	Dehydroleucodine	[39]
Cassia alata	Leaf/Hexane extract	CFA-induced arthritis/Oral administration	Rat	↓RA with ↓swelling and ↓cartilage degradation in the knee joint and ↓leucocyte of synovial fluid	–	[42]
Clematis chinensis	Root/-	Collagen-induced arthritis/Oral administration	Rat	Anti-arthritic activity via ↓TNF-α, ↓IL-1β levels in peripheral blood and ↓COX-2 in synovial membrane	Triterpene saponin (AR-6)	[51]
Clematis vitalba L.	Aerial parts/Hydroalcoholic extract	Carrageenan-, serotonin- and PGE2-induced paw oedema and CFA-induced arthritis/Oral administration	Mouse	↓Paw oedema in all models and ↓arthritis and oedema of knee joint	C-glycosylflavon, 4′-O-coumaroyl-isovitexine or vitalboside	[50]
Colchicum luteum	Corm/Hydroalcoholic extract	Formaldehyde – and CFA-induced arthritis/Oral administration	Rat	↓Joint swelling and ↓arthritis in both model via ↓IL-6, ↓IL-1β and ↓TNF-α	–	[53]
	Corm/Hydroalcoholic extract	Cotton pellet-induced granuloma formation and carrageenan-induced paw oedema/Oral administration	Rat	↓Granuloma formation and ↓paw oedema through ↓IL-6, ↓IL-1β and ↓TNF-α	–	[54]
Ferula hermonis	Root/Dichloromethanic extract	Carrageenan-induced paw oedema/Oral administration	Rat	↓Paw oedema	Ferutinin, teferin and teferidin	[57]
Inula viscosa	Aerial part/Dichloromethanic extract	TPA-induced ear oedema and PLA2-induced paw oedema/Topical administration	Mouse	↓Ear and paw oedema	3-acetyl-7-O-methylaromadendrin, sakuranetin, 7-O-methylaromadendrin and sakuranetin	[63]

Table 3 (*Continued*)

Plant	Part/extraction	Method/route of administration	Animal	Result	Active constituents	References
Smilax china	Rhizome/Methanol extract	Carrageenan-induced paw oedema/Oral administration	Mouse	↓Paw oedema by ↓LOX	Sieboldogenin	[73]
Smilax glabra	Rhizome/Ethanolic extracts	Carrageenan-induced paw oedema/Oral administration	Rat	↓Paw oedema by ↓leucocyte migration	–	[72]
	Rhizome/Aqueous extract	Adjuvant-induced arthritis/Oral administration	Rat	↓Arthritis and ↓swelling with ↓activated macrophages	–	[71]
Strychnos nux-vomica	Seed/Alkaloid fractions	Carrageenan-induced paw oedema, acetic acid-induced vascular permeability and CFA-induced arthritis/Intraperitoneal administration	Rat	↓Paw oedema by↓PGE2, ↓vascular permeability, ↓arthritis by ↓6-keto-PGF1a and ↓5-HT in rat's blood plasma	Brucine and brucine N-oxide	[75]

TPA,12-O-tetradecanoylphorbol-13-acetate; MPO, Myeloperoxidase; CFA, complete Freund's adjuvant; IL-6, interleukin-6; PGE2, prostaglandin-E2; PGF, prostaglandin-F; IFN-γ, interferon- γ; TNF-α, tumour necrosis factor-alpha; NF-κB, nuclear factor κB; NO, nitric oxide; MDA, malondialdehyde; COX1, cyclooxygenase-1; iNOS, inducible NO synthase; ND, not determined; LT-B4, leukotriene-B4; EPP, ethyl phenylpropiolate; 5-HT, 5-hydroxytryptamine; LOX, lipoxygenase.

Table 4 Clinical studies on medicinal plants traditionally used for the treatment of RA

Plant	Preparations/Route of administration		Study design	Disease	No. of patients	Treatment duration	Result	References
	Treatment group	Control group						
Clematis mandshurica	Capsule 200 mg (TID) containing *Clematis mandshurica, Trichosanthes kirilowii,* and *Prunella vulgaris*/Oral administration	Celecoxib 200 mg (BID)	Multicentre, randomized, double-blind, double-dummy, Phase III, noninferiority controlled clinical trial	Patients with rheumatoid arthritis	183	6-week	No significant difference between response rate of plant and control group indicating the herbal capsule was as efficacious as celecoxib. No serious adverse effects were observed.	[52]
Nigella sativa	*Nigella sativa* oil capsules/ Oral administration	Placebo	A placebo-controlled study	Patients with rheumatoid arthritis	40	1-month	↓Disease activity score significantly, ↓number of swollen joints and improvement in the duration of morning stiffness ($P = 0.017$)	[81]

TID, tree times per day; BID, two times per day.

inhibitor of NF-κB (IκB), resulting in the nuclear migration of NF-κB binding to DNA, and stimulates cytokine genes expression. Suppression of IκBα phosphorylation and degradation in cytoplasm of human mast cell by scopoletin has a pivotal role in anti-inflammatory potential of this natural remedy.[28]

Likewise, scopoletin improves histological architecture of arthritic joints, limits synovial hyperplasia, reduces the formation of new blood vessel within the synovial tissues and inhibits erosive changes in the bone and cartilage. Synovial macrophages are stimulated to secrete vascular endothelial growth factor (VEGF), which binds to specific receptors on local endothelium and initiates angiogenesis and migration into the joint cavity, with a resultant enhancement in vascular permeability.[29] Deregulated expression of VEGF in RA suggests a potential role for VEGF in the disease pathogenesis. There is considerable interest in targeting angiogenesis and its related growth factors to discover novel therapeutic approaches for successful protection and treatment of RA. A high dose of scopoletin reduces the overexpression of VEGF, basic fibroblast growth factor (bFGF)-2 and IL-6 in the synovial tissues of animals with adjuvant-induced arthritis. Thus, this natural compound possesses therapeutic benefits in RA through anti-angiogenic alterations and a decrease in neovascularization mediated by suppressing IL-6, VEGF and FGF-2 overexpression.[30,31]

Arctium lappa L. (Asteraceae)

Different species of *Arctium* have been used in traditional medicine for managing topical and systemic inflammatory conditions like rheumatoid disorders and chronic inflammatory bowel disease. Arctigenin is a lignan compound considered as one of the main constituents of *Arctium lappa* seeds. Upon inflammatory condition of RA pathogenesis, macrophages release pro-inflammatory cytokines and also nitric oxide (NO). Experimental investigations showed that arctigenin and its glycoside, arctiin, exhibit anti-inflammatory activity by suppressing a wide range of interleukins like IL-1β, IL-6, IL-4 and IL-5, as well as TNF-α. This natural compound also alleviates the level of NO, which is mediated by suppressing the activity and expression of inducible NO synthase (iNOS). The cellular mechanism of anti-arthritic and anti-inflammatory activity of arctigenin is attributed to inhibiting nuclear signalling pathway (NF-κB) and mitogen-activated protein kinases (MAPKs) phosphorylation. MAPK is a major molecular target component that increases the expression of mediators of inflammation, which are central to the pathophysiology of RA. The α-isoform is important to the intracellular signalling pathway for the generation of TNF-α or IL-1β. It also regulates the expression of COX-2, the enzyme that regulates PGE2 in inflammation.[32] Inhibitors of MAPK such as arctigenin block the production of TNF-α and IL-1β in monocytes and in synovial tissue of arthritic animals.[33–35] Likewise, the leaf of *A. minus* (Hill) Bernh. exhibits anti-inflammatory potential in animal model of carrageenan-induced paw oedema. [36]

Artemisia absinthium L. (Asteraceae)

In traditional Persian medicine, the aerial part of *A. absinthium* is one of the ancient drugs that possess medicinal effects on neuralgia, rheumatoid disorder, as well as inflammatory diseases. Scoparone, one of the main active constituents of *A. capillaris* Thunb., suppresses inflammatory cascade produced by macrophages significantly in IFN-γ- and LPS-stimulated RAW 264.7 cell mediated by reducing the release of NO and PGE2.[37] Any decrease in the level of NO is mediated by inhibition of iNOS expression. Likewise, inhibition of COX-2 expression by scoparone has a pivotal role in reduction in inflammatory reaction mediators.[37] Expression of COX-2 and synthesis of cytokines, such as TNF-α, IL-1β, IL-6 and IL-8, in RA condition is mediated by nuclear signalling pathway.[38]

Aerial parts of *A. sylvatica* Maxim. and *A. douglasiana* Besser suppress nuclear signalling pathway (NF-κB), so they play an important role in the reduction in RA symptoms.[37,39] Phytochemical investigations have shown that numerous chemical constituents are considered as responsible agents for anti-arthritis and anti-inflammatory potentials of *Artemisia* spp including, artemisolide, 3-methoxytanapartholide, deacetyllaurenobiolide, moxartenolide, arteminolides, dehydroleucodine, scopoletin, scopolin and esculetin.[37,40,41]

Cassia angustifolia M. Vahl (Fabaceae)

Cassia angustifolia is one of the important traditional remedies used for clinical symptoms of RA. There is no scientific evidence on the efficacy of this species in managing rheumatoid disorders. However, the leaf of *C. alata* L. improves RA symptoms, including swelling, and cartilage degradation, and inhibits leucocyte infiltration into synovial fluid of rat knee joint.[42]

Citrus medica L. (Rutaceae)

Citrus medica commonly known as citron is cultivated worldwide, and the peel, leaves and root have been used in folk medicine of Asian nations particularly India and Iran. In traditional medicine, this natural drug is suggested to be useful for the treatment of rheumatism, hepatitis and arthritis. It has been confirmed that the fruits possess antioxidant and anti-inflammatory activity. The peels of *C. medica* and fruits of *C. unshiu* (Swingle) Marcow.

suppress inflammatory response in rheumatoid condition. These natural remedies execute anti-inflammatory activity in terms of suppressing inflammatory cytokines such as TNF-α, PGE2, IL-1β, as well as IL-6, which regulate different vascular and intercellular cell adhesion agents, leading to the recruitment of leucocytes to sites of inflammation. Citrus fruits also inhibit the release of NO via suppressing the expression of iNOS enzyme. Limonene as one of the active agents of *C. medica* is effective in inhibiting the production of NO and decreases the expression of iNOS and COX-2 proteins. It also decreases the expression of TNF-α, IL-1β and IL-6.[43–45] The inhibitory effect of this medicinal plant on pro-inflammatory cytokines and mediators is mediated by suppressing the nuclear signalling pathway.[45]

MAPK pathway is considered as one of the most broadly investigated cellular signal transduction pathways regulating inflammatory process in arthritic condition. In vitro investigations have shown that this transduction pathway possesses a crucial role in modulating iNOS and COX-2 enzymes expression, as well as stimulating the production of RA-associated cytokines in macrophages and synovial cells. In addition, TNF-α, IL-1 and IL-6 are the major inducers of extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK activation in cultured human synovial cells. Citrus constituents possess therapeutic effects on RA-associated inflammation via reducing the phosphorylation of MAPK subsets, JNK and ERK.[45,46]

Clematis ochroleuca Aiton (Ranunculaceae)

Clematis ochroleuca is traditionally used for several rheumatoid disorders as RA. Saponin-enriched extracts from the root of *C. chinensis* Osbeck possess a significant therapeutic potential on LPS-stimulated acute inflammatory arthritis in rabbit. This natural plant can significantly elevate matrix collagen II levels in the immunohistochemical assay in animal models. Likewise, the saponin fraction encompasses preventive effects on monosodium iodoacetate-induced animal arthritis. Macrophages of synovial tissue trigger matrix metalloproteinase (MMP)-3-associated cartilage damage. The saponin compounds exhibited inhibitory effects against LPS-stimulated overexpression of MMP-3 and MMP-13, indicating its benefits in inflammatory-associated joint degradation. Wen *et al.* showed that liposome cream from this medicinal plant alleviated arthritic complication as well as the levels of IL-1β and TNF-α in the synovial fluid of arthritic rabbits stimulated by intra-articular injections of papain. Positron emission tomography (PET) imaging has confirmed the therapeutic potential of this remedy in animal model of RA. It significantly reduces 2-18F-fluoro-2-deoxy-d-glucose (18F-FDG) uptake in terms of standard uptake value being assessed by PET uptake in the animal arthritic joints. Reduction in the PGE2 level in primary human chondrocytes mediated by suppressing COX-2 expression is among the main contributors in its anti-arthritic potential.[47–49]

The root of *C. mandshurica* Rupr. exhibits a remarkable anti-inflammatory activity. The roots significantly lower LPS- and IFN γ-stimulated PGE2 and NO production in mouse peritoneal macrophages and lessen IL-2 and IFN-γ in Con A-activated splenocytes.[47,48] In addition, triterpene saponin, C-glycosylflavon and 4′-O-coumaroyl-isovitexine are among the responsible agents for anti-arthritic potential of *Clematis* spp.[50,51] In a randomized double-blind clinical trial performed by Song *et al.*, intake of *C. mandshurica*-containing capsules improved therapeutic response in patients with RA similar to celecoxib. During the clinical trial, the plant was safe and no major adverse effect was observed.[52]

Colchicum autumnale L. (Colchicaceae)

The corm of *C. autumnale* is an important natural drug with long history of efficacious use for managing various inflammatory disorders like goat, haemorrhoid, hepatitis and rheumatism. Hydroalcoholic extract from the corm of *C. luteum* Baker exhibited remarkable anti-arthritic potential in animal model of formaldehyde-induced arthritis and was superior to indomethacin in alleviating the joint swelling during the observation period. Likewise, corm extract showed a strong therapeutic effect on complete Freund's adjuvant (CFA)-induced arthritis, which has a wide range of pathological and immunological features with human RA. The anti-arthritic potential of this remedy is mediated by inhibiting the production of pro-inflammatory cytokines TNF-α, IL-6 and IL-1β as well as the expression of TNF-R1 in the synovium. Scientific studies have confirmed that the receptor subtype, TNF-R1, is involved in pathophysiological effects of TNF-α leading to arthritic conditions.[53,54]

It has been reported that colchicine, the active phytochemical agent of *C. luteum*, suppresses pro-inflammatory cells like macrophages through its interaction with cellular tubulin protein, demonstrating that this medicinal plant obviously improves rat paw oedema symptoms including granuloma formation mediated by suppressing the inflammatory cytokines TNF-α, IL-6 and IL-1β in inflamed tissue.[53,54]

Cuscuta epithymum L. (Convolvulaceae)

Cuscuta epithymum, commonly known as dodder, is a traditional medicinal plant, which has been administered by Persian physicians for a wide range of diseases. In vitro assessment showed that methanolic extract from the seeds

of *C. campestris* Yuncker. significantly lowers the production of nitrite in activated macrophages. Quercetin as one of the main active constituent in the seeds of *C. campestris* plays a critical role in anti-inflammatory potential of this plant. Lee *et al.*[55] reported that processed seeds have higher level of quercetin leading to enhancement of inhibiting inflammatory reaction in RAW264.7 cells. Likewise, *C. reflexa* Roxb. inhibits NF-κB binding to its relevant motif and consequent initiating transcription activity, which leads to regulating various inflammatory signalling pathways. It is confirmed that downregulation of the cytokines involved in inflammatory arthritis, COX-2 and TNF-α, by treatment of this natural agent is mediated via suppressing NF-κB expression.[55,56]

Ferula asafoetida L. and *F. persica* L. (Apiaceae)

The oleo-gum resin of both *F. assa-foetida* and *F. persica* is among the important remedies of traditional Persian medicine, which has been used for various disorders particularly inflammatory illnesses. Experimental study showed that the active phytoconstituents, ferutinin and teferin play a central role in improvement in inflammatory response by *Ferula* species.[57] Ferutinin, a phytoestrogen compound which is abundant in *Ferula* genus, has a strong osteoprotective activity. Daily intake of ferutinin for 2 months significantly prevents osteoporosis due to estrogen deficiency in ovariectomized rats. Histomorphometrical assessment of trabecular and cortical bone from femur and lumbar vertebrae has demonstrated that this natural molecule has higher anti-osteoporotic effect than estradiol benzoate on bone mass.[58] Methyl 3,5-*O*-dicaffeoylquinate and 3,5-*O*-dicaffeoylquinic acid from the flower of *F. lutea* Poir. significantly inhibit 5-LOX enzyme, which catalyses the dioxygenation of polyunsaturated fatty acids to produce Hydroperoxyeicosatetraenoic acids and Hydroxyeicosatetraenoic Acids.[59,60] Crude extract from *F. persica* and isolated active ingredients, persicasulphide and umbelliprenin, significantly inhibit MMP-2 and 9, a family of endopeptidase which regulates destruction of extra cellular matrix and is involved in inflammatory arthritis.[61]

Inula helenium L. (Asteraceae)

Inula helenium commonly known as horseheal is a perennial plant with various medicinal indications in folk and traditional medicine. Dihydroflavonols elicited from aerial part of *I. viscosa* L. including sakuranetin, 7-O-methylaromadendrin, 3-O-acetylpadmatin and 3-acetyl-7-O-methylaromadendrin have demonstrated both *in vitro* and *in vivo* anti-inflammatory activity. Dihydroflavonol compounds of *I. viscosa* significantly suppressed the metabolism of arachidonate in rat peritoneal leucocytes, which is stimulated by cation ionophore.[62,63] Given the fact that arachidonic acid through COX pathway is metabolized into thromboxane A2 and PGs, and also via the LOX pathway metabolized into leukotrienes, Hydroperoxyeicosatetraenoic acids and Hydroxyeicosatetraenoic Acids, biosynthetic cascade of arachidonic acid possesses a pivotal role in several pathological conditions as inflammatory reaction or arthritis.[3,5] Likewise, the flavonoid components of *I. viscosa* remarkably reduce the production of leukotriene (LT)-B4, *in vitro* in rat peritoneal leucocytes. Among the dihydroflavonols, sakuranetin can inhibit the activity of 5-LOX *in vitro*.[62–64]

Elastin is a key extracellular matrix protein, which has a mechanical effect on different tissues like ligaments, arteries and skin. Neutrophil elastase is a proteolytic enzyme, with the potential to degrade fibrous, fibronectin and cartilage proteoglycans. Therefore, elastase is a key contributor in the pathology of RA. Hernández *et al.*[63] reported that sakuranetin and 7-O-methylaromadendrin can significantly decrease the elastase release and suppress the activity of elastase enzyme.

The sesquiterpenoid compounds, ilicic acid and inuviscolide, from *I. viscosa* demonstrated inhibitory effect on phorbol ester- or ethyl phenylpropiolate-induced ear oedema as well as the phospholipase (PL)A2- or serotonin-induced paw oedema.[62] In addition, sesquiterpene lactones like ergolide and granilin isolated from *I. falconeri* Hook. f. aerial part exhibit inhibitory effect on NO production in RAW264.7 macrophages.[63,64]

Nigella sativa L. (Ranunculaceae)

The seeds of *N. sativa*, commonly known as kalonji or black caraway, grow in south and south-west Asia. The seeds have traditionally been administered by the physicians of Middle and Far East as a medicinal remedy for managing various diseases. In a placebo-controlled clinical trial reported by Gheita and Kenawy, intake of *N. sativa* oil reduced clinical signs of RA including the number of swollen joints and disease activity score in patients with RA.[81]

The seeds of *N. sativa* exhibited ear and paw oedema alleviation in animal models.[66] Thymoquinone, the major active compound derived from *N. sativa*, is a bioflavonoid with strong anti-inflammatory, antioxidant, neuroprotective, as well as anticarcinogenic effects. In vivo studies exhibited the ability of thymoquinone for managing inflammatory-associated diseases; 21-day administration of thymoquinone in Wistar rat with collagen-induced arthritis demonstrated anti-arthritic effects and significantly improved clinical signs of joints. This substance reduces articular elastase and myeloperoxidase (MPO) activity. MPO is released from stimulated granulocytes within the

inflammatory condition and is directly associated with the activity and accumulation of leucocytes in the arthritic joints. Thymoquinone also suppresses the expression of pro-inflammatory cytokines including IL-1β, TNF-α, IL-10, IFN-γ, PGE2 and IL-6, which are highly expressed in the rheumatoid joint and are a key contributor in the pathogenesis of RA. In addition, antioxidative damage is another mechanism of *N. sativa* constituents in improving rheumatoid disorders through elevating the activity of antioxidant enzymes as well as inhibiting the products of lipid peroxidation and NO.[65–68]

Rheum palmatum L. (Polygonaceae)

Preclinical studies have shown that the root of *R. palmatum* demonstrates strong anti-inflammatory activity. Emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) is an anthraquinone component derived from rhizomes and roots of *R. palmatum* with a strong potential to inhibit the overexpression of inflammatory agents including TNFα, iNOS and IL-10 as well as NF-κB p65. This molecule can significantly suppress the proliferation of RA synoviocytes, which are induced by IL-1β as well as LPS under hypoxic condition. Hypoxia is defined as a pathological situation with deficient oxygen supply, resulting in the stimulating transcription factor hypoxia-inducible factor 1 (HIF-1) and also VEGF. Literature evidence has shown that VEGF is obviously elevated in RA synovial fluid with a specific role in angiogenesis of rheumatoid joints. Emodin remarkably suppresses hypoxia-associated RA through reducing the overexpression of HIF-1 and VEGF. Likewise, this natural molecule suppresses the expression of pro-inflammatory cytokines like TNF-α, IL-6, IL-8 and PGE2, which is mediated by inhibiting the expression and activity of COX-2 in the rheumatoid condition, indicating its therapeutic action on RA progress.[69,70]

Accumulated evidence suggests that MMPs released from synoviocytes are associated with joint destruction in rheumatoid pathogenesis. Intervention with both IL-1β and LPS has obviously stimulated upregulation of MMP-1 and MMP-13 expressions in synoviocytes suppressed by emodin. It has been confirmed that the intracellular signalling pathways, p38 MAPK and NF-κB, are involved in the transcriptional activation of MMP expression. However, the potential of emodin in suppressing MMP-1 and MMP-13 is not related to MAPK and NF-κB pathways.[69,70]

Histone deacetylases (HDACs) encompass a class of enzymes with modulatory effect on inflammatory cascade and MMP function in synoviocytes. It has been found that attenuation of HDAC activity – particularly HDAC1 – is among the main mechanisms of emodin in managing IL-1β- and LPS-induced RA in hypoxic condition.[69,70]

Smilax china L. and *S. glabra* Roxb. (Smilacaceae)

The rhizome of *S. china* and *S. glabra* has a long history of use for inflammation, gastric tonic, goat, haemorrhoid, as well as joint disorders in Persian medicine. Several pharmacological studies have shown anti-inflammatory, anticancer and antinociceptive activity of this plant. In traditional Chinese medicine, this remedy has various therapeutic effects, particularly chronic pelvic inflammation. Experimental studies on animal models of inflammation have confirmed the anti-inflammatory potential of this natural drug, which is mediated by attenuating the overexpression of pro-inflammatory mediators, TNF-α, NO and IL-2. In addition, regulation of nuclear signalling NF-κB is the possible mechanism of its anti-arthritic effect. T lymphocyte has a significant role in immunological events of pathological processes in RA. In vitro studies have revealed that this remedy can significantly inhibit the proliferation of T lymphocyte.[71,72] In addition, *S. glabra* has exhibited improvement in RA symptoms through inhibiting leucocyte migration and suppressing activated macrophages *in vivo*.[71–73]

Seiboldogenin is a steroidal saponin, which is derived from ethyl acetate fraction of the *S. china* and *S. glabra* crude extract. It has been reported that seiboldogenin has modulatory effect on biphasic inflammatory reactions including early phase of the inflammation through suppressing the release of histamine and serotonin as well as later phase of inflammatory response mediated by regulating the activity of kinin-like agents, proteases and PGs, in animal models.[74] Inhibitory potential of this molecule on LOX indicates its ability to manage inflammatory conditions as RA.[71,73]

Strychnos nux-vomica L. (Loganiaceae)

One of natural drugs, which has traditionally been used for inflammatory disorders, especially rheumatoid condition, is *S. nux-vomica.* In traditional medicine, this plant is assumed to have palliative effect on rheumatic pain. Experimental investigations have shown that the seeds of *S. nux-vomica* possess anti-inflammatory activity in terms of suppressing PGE2 and decreasing vascular permeability. Brucine and brucine N-oxide are two natural alkaloids, which are isolated from the seeds of *S. nux-vomica*.[75,76]

In hot-plate and writhing test, the alkaloids of *S. nux-vomica* has shown protective effect on thermic and chemical stimuli. Their analgesic activity has been long lasting in comparison with pethidine. Likewise, the alkaloids have demonstrated inhibitory effect on carrageenan-induced rat paw oedema.[77] Brucine and brucine N-oxide

remarkably alleviate clinical signs of CFA-induced RA mediated by reducing the levels of 6-keto-PGF1a. 5-Hydroxytryptamine (5-HT) is expressed in excited sensory neurons of inflammatory sites and is a key contributor in the sensation of pain from arthritic joints. Brucine and brucine N-oxide significantly decrease the levels of 5-HT in CFA-induced arthritis rat's blood plasma and elevate 5-hydroxytryindole-3-acetic acid, the main metabolite of degradation of 5-HT by MAO, indicating role of MAO activity in regulating 5-HT pathway by these natural agents.[75,77]

Brucine and brucine N-oxide obviously suppress the release of PGE2 in inflamed tissue and reduce levels of 6-keto-PGF1a in blood plasma, with no significant effect on the level of thromboxane B2. Therefore, the mechanism of action of the alkaloids is not entirely similar to NSAIDs.[75]

For some of the medicinal plants traditionally been used for the management of RA including *Astragalus arbusculinus* Bornm. & Gauba (Fabaceae), *Convolvulus arvensis* L. (Convolvulaceae), *Dolichos lablab* L. (Fabaceae), *Dorema ammoniacum* D. Don. (Apiaceae), *Narcissus tazzeta* L. (Amaryllidaceae), *Nepeta menthoides* Boiss. & Buhse (Lamiaceae), *Opopanax chironium* W.D.J.Koch (Apiaceae) and *Peganum harmala* L. (Nitrariaceae), no scientific evidence was observed. Cellular and preclinical

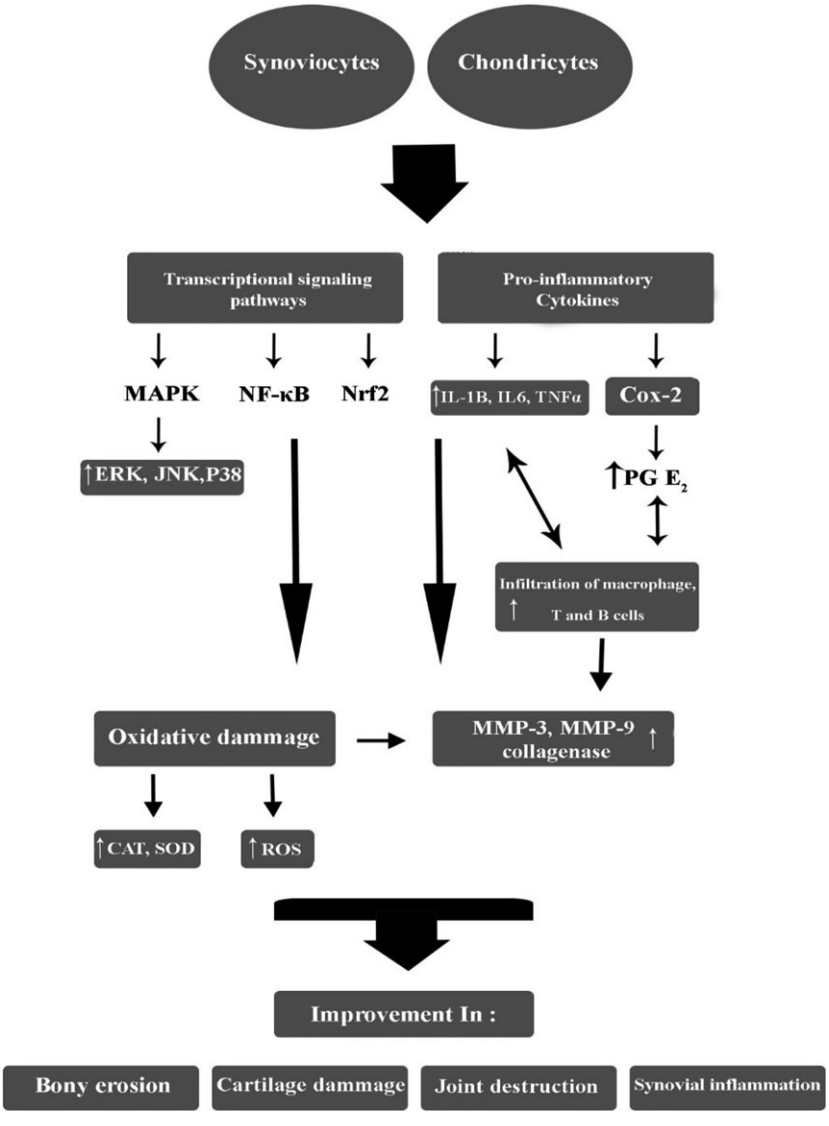

Figure 1 Possible biochemical pathways and mechanisms in the pathogenesis of rheumatoid arthritis where medicinal plants can have an effect. MAPK, Mitogen-activated protein kinase; NF-κB, nuclear factor κB; Nrf2, nuclear factor E2-related factor 2; IL-1β, Interleukin-1β; TNF-α, tumor necrosis factor-alpha; COX1, cyclooxygenase-2; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; PGE2, prostaglandin-E2; MMP, matrix metalloproteinases; CAT, catalase; SOD, superoxide dismutase; ROS, reactive oxidative species.

studies for scientific evaluation of the efficacy of these remedies are required.

Discussion and Conclusion

This review assessed the evidence and molecular mechanisms of medicinal plants used for the treatment of RA in traditional Persian medicine. In addition, active phytochemical agents of these plants for plating future natural drugs were discussed.

Investigations have indicated that people suffering from chronic debilitating diseases and also patients dissatisfied with conventional treatments often seek alternative treatments. Traditional and folklore approaches for the management of diseases are among the main alternative sources of medicine. However, in spite of the growing level of

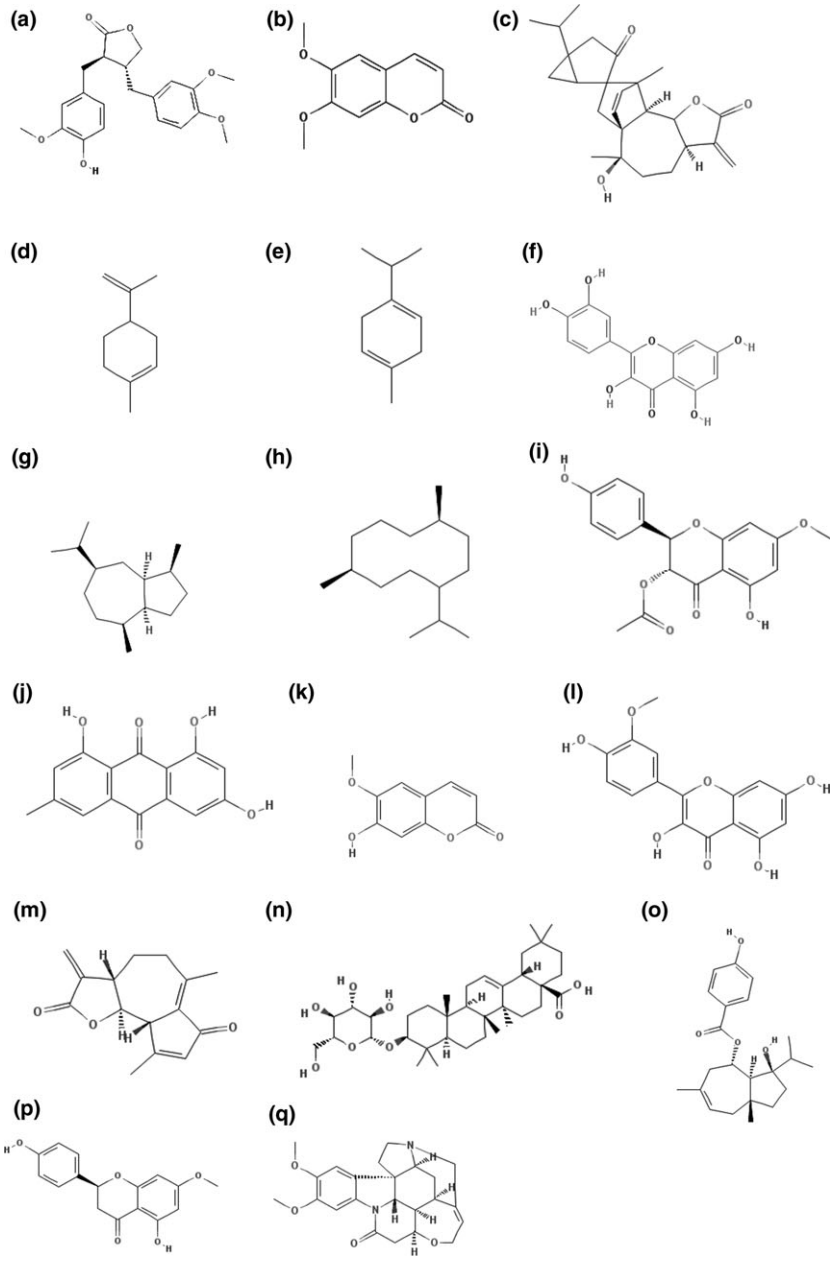

Figure 2 Chemical structures of principle components of medicinal plant traditionally used for management of RA in Persian medicine. a: Arctigenin, b: Scoparone, c: Artemisolide, d: Limonene, e: γ-terpinene, f: Quercetin, g: Guaiane, h: germacrane, i: 3-acetyl-7-O-methylaromadendrin, j: Emodin, k: Scopoletin, l: isorhamnetin, m: Dehydroleucodine, n: vitalboside, o: Ferutinin, p: sakuranetin, q: Brucine.

tendency towards traditional medicine, evidence for safety and effectiveness of these alternative medicines is limited.[78–80] Although conventional treatments of RA commonly alleviate the symptoms, high incidence of adverse reactions of these drugs has resulted in exploration of alternative methods, particularly traditional remedies, for symptomatic relief of RA.

Numerous medicinal plants have traditionally been used for the management of RA in Persian medicine. Various experimental studies on these medicinal plants were gathered, and efficacious and pharmacological aspects of this natural therapy were presented. These studies comprise cell, animal and human studies, which are summarized in details in Tables 2, 3 and 4, respectively.

Scientific evidence has revealed that traditional medicaments exert beneficial effects on RA through several cellular and molecular mechanisms including downregulation of pro-inflammatory cytokines such as IL-12, IL-2, IL-8, TNF-α, IFN-γ, IL-1α, IL-6 and IL-8 as well as inhibiting initiation of inflammatory response. It is suggested that some traditional natural agents targeting these cytokines act as anti-IL-1 receptor antagonist and anti-TNF inhibitors. Accumulated evidence has shown the association between oxidative stress in pathological processes of inflammatory arthritis and rheumatoid disorders and excessive generation of free radicals and oxidants in arthritic joints.[81–83] Therefore, suppression of oxidative-associated damage of arthritic tissue mediated by attenuating free radicals and NO as well as downregulation of iNOS expression is among the anti-arthritic mechanisms of natural remedies in traditional Persian medicine. Likewise, enhancement of antioxidative performance through stimulating the expression and activity of antioxidant enzymes including catalase, SOD and GPx is another mechanism of the natural remedies (Figure 1).

Matrix metalloproteinases (MMPs) consist of more than 20 proteinases, which are expressed abundantly in chondrocytes and synovial cells within arthritic joints and have a principal role in the degradation of the matrix in RA.[84] It has been found that traditional natural agents inhibit cartilage degradation through downregulation of destructive metalloproteinases (e.g. MMP-9, MMP-3). Results of the current review article show that modulation of transcriptional and transduction signalling pathways including NF-κB and MAPK, with upstream regulatory activity on inflammatory as well as oxidative stress cascade, plays a central role in therapeutic potential of natural remedies on pathological condition of RA.

The results of *in vitro* and preclinical studies are preliminary; nevertheless, they suggest the promising potential of mentioned natural drugs in the improvement in the associated symptoms of RA. In addition, good tolerance of most of the herbal remedies along with the long history of consumption in traditional medicine was demonstrated. However, nonclinical studies are mandatory to determine the toxicity profiles of almost all medicinal plants in common use for the management of RA.

Based on reviewed cellular and animal studies, various active phytochemical agents derived from mentioned medicinal plants are potentially efficacious on RA. These phytoconstituents are from different chemical categories including flavonols (quercetin), lignans (arctigenin), coumarins (scopoletin and scoparone), oxyanthraquinones, terpenes (limonene), triterpene saponin, steroidal saponin (seiboldogenin), glycosylflavons, phytoestrogens (ferutinin), sesquiterpenes (umbelliprenin), sesquiterpenoid (ilicic acid and inuviscolide), sesquiterpene lactones (ergolide and granilin), dihydroflavonols (sakuranetin and 7-O-methylaromadendrin), anthraquinones (emodin), alkaloids (brucine and brucine N-oxide), as well as thymoquinone. Figure 2 illustrates the chemical structures of the principle components of medicinal plants traditionally been used for the management of RA in Persian medicine. Further research is mandatory to focus on bioefficacy and safety aspects of these phytochemical agents for finding novel natural drugs.

To conclude, numerous *in vitro*, preclinical and clinical studies have confirmed the beneficial effects of traditionally used medicinal plants for the management of RA pathogenesis and its complications in traditional Persian medicine. Limited human studies suggest that traditional medicinal plants used for RA have less adverse effects than conventional drugs. Results obtained from pharmacological studies indicate a necessity to establish bioefficacy, optimum dosage and duration of treatment. Further well-designed human clinical trials are required to evaluate the effects of traditional natural remedies in terms of symptomatic, functional and biological outcomes. Current natural agents may also be tested as adjunctive therapies in combination with conventional drugs for RA.

Declarations

Conflicts of interest

Authors have no conflict of interest.

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