Acta Biologica Marisiensis sciendo

MEDICINAL PLANTS FROM THE FLORA OF ROMANIA BENEFICIAL IN OSTEOARTHRITIS AND RHEUMATIC ARTHRITIS

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Received: 6 December 2022; **Accepted:** 13 December 2022; **Published:** 30 December 2022

Abstract: In this study, we focus on two arthritic diseases that affect a large part of the population, which cause inflammatory disorders of the joints and oxidative stress, which can cause certain degrees of disability. Arthritis is a chronic disease frequently encountered in the world's population. Osteoarthritis, and rheumatoid arthritis, autoimmune and inflammatory conditions, are two extensive forms of arthritis associated with pain, swelling, and stiffness in the joints and a low standard of life. Many drugs are used in their treatment, associated with some severe side effects and expensive prices. Today there are many studies carried out with extracts from medicinal plants, used in alternative therapy, and effective in these diseases. They are available for clinical use due to the active phytoconstituents that modulate inflammation and are antioxidants. In carrying out this study, electronic databases were screened: Science Direct, PubMed, and Google Scholar, trying to describe these medicinal plants, and elucidate their biological mechanisms of action. The most numerous references were found on the following plants: *Arctium lappa*, *Glycyrrhiza glabra*, *Nigella sativa*, *Urtica dioica*, etc. vary parts of plants are used such as different types of seeds, roots, leaves, fruit, bark, flowers, or even the whole plant.

Keywords: osteoarthritis; rheumatoid arthritis; medicinal plants; bioactive compounds

1. Introduction

Medicinal plants are an important natural wealth of the Earth. More than 20,000 plants from around the globe have medicinal or aromatic properties, even if only a tenth of them are currently used. The beginnings of their knowledge and use overlap with the beginnings of the rise of man, who turned to the healing properties of various plants, to relieve pain. The main remedies were almost entirely based on phytotherapy, so the foundations of rational medicine are found in folk medicine. This knowledge was transmitted, at first, orally and then in writing, in man's effort to prolong his life. In Romania, out of the c. 3,800 spontaneous plants (Sârbu et al., 2013), over 850 are used in traditional medicine. Out of these, about 300 are studied from a chemical-pharmaceutical point of view (Oroian, 2011).

One of the most common chronic articular diseases, osteoarthritis (OA) results from the destruction of articular cartilage and

subchondral bone (Kang et al., 2019). The major cause of OA is the disruption in the equilibrium between cartilage synthesis and degradation of joint cartilage. OA is considered an age-linked chronic condition with complex pathogenesis and without an effective and definitive method for its cure or, at least, management. Future studies need to sort out the mechanisms mediating the commencement and evolution of OA (Zhang et al., 2015; Gregori et al., 2018).

Considering that regular medication for OA does not have huge success and has a lot of side effects, in recent years, natural products that are known to have anti-inflammatory properties became broadly studied (Sharkey et al., 2021). Numerous herbs have been evaluated with well-documented studies. They proved to have encouraging potential for controlling pain and improving the evolution of arthritic conditions (Lindler et al., 2020; Anvari et al., 2020; Banic et al., 2021; etc.).

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that has a progressive evolution. It can cause disability, and increase the risk of cardiovascular illness. RA is frequently related to increased levels of oxidative stress and inflammatory mediators (Lindler et al., 2020).

Our study gathers data about medicinal plant species present in Romanian flora, which can serve to further studies to establish the mechanism and action of these extracts in osteoarthritis and rheumatoid arthritis treatment.

2. Materials and methods

To collect the bibliographic data edited in the past 10 years (2012-2022), Science Direct, PubMed, and Google Scholar web search engines were used. We took into consideration the following keywords: medicinal herbs, bioactive compounds, osteoarthritis, rheumatoid arthritis, and a combination of them.

Information about the systematic classification, the part of the plant used, the dosage form, the major constituents of the plant extract, and the mechanism of action is presented. The parts of medicinal plants that are used are different types of seeds, roots, leaves, fruit, bark, flowers, or even the whole plant. The drug is noted in Latin (Oroian, 2011; Eșianu, 2016). The components of these plants can be used in different extract forms: Ethanolic, Methanolic, Hydroalcoholic, Aqueous extract, Petroleum ether extract, Hexane/ethanolic extract, etc.

The species name and the taxonomy are consistent with Euro+Med (2006+) and Sârbu et al. (2013). The species are listed in alphabetical order.

3. Results and discussions

Considering the bioactive compounds from herbal medicines used in the treatment of OA and RA 62 species that can be found in Romania's flora were identified, belonging to 38 families (**Table 1**). The most representative families are Asteraceae, Ranunculaceae, Solanaceae, etc. Among the medicinal plants selected, the most numerous data refer to the species: *Arctium lappa*, *Arnica montana*, *Glycyrrhiza glabra*, *Nigella sativa*, *Sesamum indicum*, *Symphytum officinale* (**Fig. 4**), *Urtica dioica*, *Coriandrum sativum*, etc. All these species have anti-inflammatory properties.

Leaves, roots, bark, fruits, seeds, flowers, or even the whole plant can contain active ingredients conferring medicinal properties to that plant. Many studies on herbs and their composition isolated the active compounds and documented their role in the biological effects. Among these, we mention phenolic acids, phenylpropanoid ester, triterpene glycosides, phthalides, flavonoids, alkaloids, triterpenoid

saponin, diterpene, and triterpene. New treatment opportunities for OA and RA patients can be obtained by having a good comprehension of the mechanism of action of the herbs and their compounds.

The main bioactive compounds with anti-OA and anti-RA activities in the medicinal plants identified in Romania's flora are flavonoids, essential oils, saponins, mucilages, alkaloids, iridoids, phenolic glycosides, etc.

Flavonoids (Quercetin, Hesperidin, Baicalin, Aglycone, Gentakwanin Hydroxygenkwanin, Luteolin, Apigenin, Liquiritin, Kaempferol, etc.) have antioxidant, anti-inflammatory, anti-edematous and immunomodulatory properties. These effects are explained by the property of flavonoids to inhibit the chemical mediators responsible for inflammation. Comparing the flavonoids to other active phytocompounds proves they have broader action and relatively lower toxicity. (Eșianu, 2016; Oroian, 2011) Among the plant drugs rich in flavonoids, we mention: Rutae herba, Sambuci flos, Betulae folium, etc. (**Table 1**).

Alkaloids are very widespread in the world of cormophytes. More than 12,000 alkaloids have been identified to date, with an estimated 10-15% of cormophytes containing alkaloids. (Sinomenine, Nicotine, Berberine, Koumine etc.). They act on the cytokines IL-6, IL-12, IL-1α, TNF-α, IL-1β, and IL-10 by regulating their level and have especially immunomodulatory effect. Among the plant drugs rich in alkaloids we mention Ephedrae herba Colchici bulbus et semen, Capsici fructus (contain non-heterocyclic alkaloids), Chelidonii herba, Chelidonii radix, Boraginis semen, Symphyti radix (pyrrolizidine alkaloids) (Eșianu, 2016; Oroian, 2011)

Triterpene saponins are widespread in the plant world, being concentrated in cell vacuoles. Saponins contained in plant drugs such as Liquiritiae radix, Equiseti herba, Hedere folium, are: asiaticoside, araloside A, medecassoside, pedunculoside. These have antirheumatic effects acting in fibroblast-like synoviocytes having immunostimulatory properties (Eșianu, 2016). Similarly, Mucilages (heteropolysaccharides) are also present in herbal drugs with anti-inflammatory effects in arthritic diseases. Among the herbal drugs rich in mucilage we mention Althaeae radix et folium, Lini semen, Plantaginis folium, etc.

Most of the studies analyzed were made in vitro and highlighted the anti-inflammatory effect of the medicinal herb extracts. Moreover, the antioxidant properties of biological compounds proved to have an impact on the treatment of OA and RA.

Several plant extracts presented in this paper proved to be good assets for pain reduction and improved mobility. The risk of side effects in arthritic subjects turned out to be lower. These results warrant further investigation (Choudhary et al., 2015; Ulbricht et al., 2014; Dragoș et al., 2017; etc.)

In the checklist of medicinal plants, they are presented in alphabetical order (**Table 1**). The data recorded provide us with information on scientific name, family, common name, the part(s) used, the form of use, major phytoconstituents, therapeutic activity, mechanism of action, and references.

Most of the plant species listed in **table 1** are from the native flora of Romania, but we have also recorded a few cultivated species: *Allium cepa, Allium sativum, Althaea rosea, Capsicum annuum, Coriandrum sativum, Elaeagnus angustifolia* (**Fig. 1**), *Linum usitatissimum, Lonicera japonica, Ocimum basilicum, Ruta graveolens, Sesamum indicum*, etc. which have been intensively studied from a pharmacological point of view, being then included into the composition of some medicines.

Fig. 1. *Elaeagnus angustifolia*

Fig. 2. *Ricinus communis*

Romania's flora is rich in medicinal plants used in arthritis. Thus we mention some of them known to have strong anti-inflammatory or analgesic effects. Thus, *Nigella sativa* - Black cumin (Nigellae semen) is considered a potential candidate in the management of arthritis, *Reynoutria japonica* - Japanese knotweed (Reynoutriae radix) a good anti-inflammatory or *Glycyrrhiza glabra* - Licorice (Liquiritiae radix - officinal in Ph. Eur. and FR X) containing flavonoids, flavones, flavonals, isoflavones, etc. with antioxidant, antibacterial and anti-inflammatory activities, *Arnica montana* - Mountain horsetail (Arnicae flos-officinal in Ph. Eur.) whose dominant active principles: phenolic and flavonoid compounds would determine the anti-arthritic efficiency, *Elaeagnus angustifolia* - Smelly willow (Elaeagni fructus) of whose extract contains Kaemferol with particular analgesic and anti-inflammatory action. We also mention the species: *Borago officinalis* – Lamb's tongue (Boraginis semen - officinal in Ph.Eur.) (Boraginis herba) whose oil contains Gamma-linoleic acid with an anti-inflammatory effect or *Symphytum officinale*- Comfrey (Symphyti radix et folium) whose extract has analgesic and anti-inflammatory properties due to allantoin, rosmarinic acid and other derivatives of hydroxycinnamic acid and mucopolysaccharides (due to the content of pyrrolizidine alkaloids, with a hepatotoxic and carcinogenic effect, internal use is not recommended, and external use is limited), etc.

In the flora of our country, there are also plants whose extracts contain toxic active principles that have good analgesic or anti-inflammatory effects (which we did not mention in the paper). We mention *Cannabis sativa* - Hemp (Cannabis herba) whose main chemical component is a resin containing cannabidiol with anti-arthritic effects through anti-inflammatory and immunosuppressive action.

Papaver somniferum – Garden poppy (Papaveri imaturi fructus/opium - officinal in Ph.Eur. and FR X) considered to be a very good analgesic (morphine, codeine, and opium abuse gives rise to drug addictions, creates mental and physical dependence).

In this study, we also have a group of plants that are used in the treatment of arthritis but which are also toxic, so their extracts should only be used under medical supervision. Among these we mention *Colchicum autumnale* - The autumn crocus (Colchici bulbus et semen), which contains colchicine and has anti-arthritic and anti-inflammatory effects. Colchicine also has a mutagenic action, which is why it has uses in genetic engineering, as a plant polyploidizer. Toxicity can pass from animals, through milk, and meat, to consumers.

That is why the pastures must be cleared of these plants.

Ruta graveolens - Rue (Rutae herba) - the polyphenolic fraction of the extract from the aerial parts have an anti-arthritic action, but at the same time it is a dangerous plant because it causes metrorrhagia and gastroenteritis; recently, its spasmolytic properties have also been highlighted.

Ricinus communis (**Fig. 2**) - Castor Bean (Ricini semen - officinal in Ph. Eur. and FR X), the seeds contain polyphenols and flavonoids with anti-inflammatory action but also contain ricin, a highly toxic substance.

We also mention the presence, of some invasive medicinal species in our country, with various origins, such as *Oenothera biennis* (North America), *Portulaca oleracea* (Asia), *Reynoutria japonica* (Eastern Asia) (**Fig. 3**), *Xanthium strumarium* (North America), etc., whose chemical composition is rich in active compounds with beneficial effects in the treatment of certain diseases. For example, *Reynoutria japonica* species with a devastating impact on the biodiversity of the habitats where it occur, stands out for its special chemical composition, because the root and leaf extracts contain active principles with special therapeutic potential. In vivo and in vitro studies determined the identification of the main compounds: resveratrol, emodin, and polydatin which can exert special therapeutic effects. That is why additional pharmacological research would be needed to highlight the benefits of this invasive species, and new experiments and human clinical evidence are needed. Recently Nawrot-Hadzik et al. (2021) reported the effects of vanicoside in particular on the inhibition of SARS-CoV-2 Mpro cells.

Joint inflammation is one of the symptoms of arthritis. The onset and evolution of it cause the destruction of the articular cartilage and stimulates the synovial membrane. A notable role in this condition plays oxidative stress, as well as the anti-inflammatory response triggered by the immune system. T cells are activated and inflammatory mediators such as cytokines and chemokines are influenced (Katturajan and Sabina, 2021).

Fig. 3. *Reynoutria japonica*

Fig. 4. *Symphytum officinale* L.

The mechanism of action of medicinal plants with anti-arthritic effect acts by influencing the signaling pathways (NF-kB, RANKL, and PI3K/Akt).

They regulate pro-inflammatory and pro-catabolic mediators such as cytokines, PGE2, MMP, ROS, and apoptotic proteins These activities can help improve OA and RA joint pain, inflammation, swelling, structure, and function with minimal adverse effects (Lindler et al., 2020).

Numerous studies on the human and animal models certify that the main mechanism of action in the alleviation of RA symptoms includes inhibition of the expression of NF-κB, IL-1β, TNF-α, IL-6, IL-8, IL-17, IL-23, chemokines, TGF-β, RANKL, RANK, iNOS, arginase, COX-2, VEGFA, VEGFR, NFATC1, and TRAP in the synoviocytes. Reduced ROS, NO, MDA, carbonyl groups, and PGE2 in the joint fluid elevated the expression of PPARα/γ. A notable role in ameliorating rheumatoid arthritis etiology has antioxidant and anti-inflammatory molecules (Arunsi et al., 2022).

The effect of medicinal plants listed in this study generally follows the validated mechanism. Most of the studies refer to the downregulation of inflammatory factors and cytokines. Other plants have antiarthritic use due to the antioxidative properties of their compounds.

Most studies have been conducted in vitro, often in mice and very rarely in human subjects.

Conclusions

In this review, we have compiled and analyzed 62 medicinal species which have active compounds with anti-OA activities. All studies demonstrate the anti-inflammatory effects of extracts containing one or more secondary metabolites and suggest their anti-arthritic efficacy.

Because the pathogenesis of rheumatoid arthritis and its immune mechanism has not been fully understood, it still requires further studies.

The potential of plant raw material is enormous therefore there are great prospects in obtaining new, more effective drugs that can become an alternative treatment for arthritis. In addition, these herbs have proven effects for a long ago and they don’t have severe side effects.

We reviewed only a small sample of herbs that modulate inflammation and are available for clinical use. The aim was to point out that they differ notably from all anti-inflammatory drugs with regard to actions and security and to provide insight into their clinical use. Not explored in this paper, but of greatest importance is the inclusion of increased amounts of plants in the diet, meaning fruits, vegetables, whole grains, nuts, herbs, and spices. These will provide abundant inflammation-modulating compounds that go a long way. in calming an inflammatory state.

Finally, we have come to the conclusion that today, the return and interest in the use of medicinal plants in the treatment of arthritis is increasing. The special effort of specialists, from several fields of study, in deciphering the factors that cause these chronic inflammatory disorders that cause serious histological alterations was found. Thus, botanists (whose purpose is to identify medicinal species, their quantitative evaluation for rational exploitation, etc.), biochemists (with a role in identifying the chemical composition of drugs, the active principles and their method of extraction, etc.), pharmacologists who have the purpose to identify the mechanisms of action of plant extracts, mechanisms that have often proven particularly effective in various in vitro or animal studies. However, today there is a dearth of human clinical evidence. It is recommended that in the coming years, special

attention be paid to clinical investigations so that animal studies can be translated into humans.

It would be very interesting and useful through future studies to determine the possibility of using some compounds with anti-inflammatory and regenerative properties, directly into the joint. This way achieves much higher concentrations in the affected joint and implicitly a stronger effect without passing through the systemic circulation; the side effects are much smaller due to the fact that the substances are difficult to absorb from the joint.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Table 1. Characteristics of medicinal plants beneficial in the treatment of osteoarthritis

Botanical name English name Family	Drugs	Dosage form	Uses	Major phytoconstituents	Effects	Mechanism of Action/	References
Actaea racemosa Black cohosh Ranunculaceae	Cimicifugae radix	Extract	Arthritis	Actein, cimigoside, steroidal terpenes, and 27-deoxyactein	Anti-inflammatory Anti-arthritic Reduce edema, bone resorption, reduce chronic arthritis pain	inhibits mRNA of cytokines IL-4, IL-5 and TNF-α	Saleem et al., 2019 Choudhary et al., 2015 Ulbricht et al., 2014 Yang et al., 2012
Allium cepa Onion Amaryllidaceae	Allii cepae bulbus	Paste	Rheumatoid Arthritis	Quercetin	Anti-arthritic	Lessen the purinergic system (E-NTPDase and E-ADA activities) and the quantities of IFN-gamma and IL-4. Depletion in leukocytosis and immune expression of TNF-α, IL-17 in the synovium. Restrain the production of proinflammatory cytokines (IL-1β, IL-6, and IL-8)	Arunsi et al., 2022 Tsai et al., 2019
Allium sativum Garlic Amaryllidaceae	Allii sativi bulbus et semen	Oil	Anti-arthritic	Diallyl sulfide	Anti-arthritic	Reduces paw edema and the levels of CRP. Suppresses the expression of TNF-α, IL-1β, IL-2, iNOS, COX-2, NF-κB, and MPO, and the production of NO, PGE2, and MCP-1. Increases the IL-10 and GSH	Arunsi et al., 2022

Althaea officinalis Marsh mallow Malvaceae	Althaeae radix, folium et flos	Aqueous extract	Rheumatoid Arthritis Anti-arthritic	Scopoletin	Anti-inflammatory	Reduce inflammation Suppress the release of PGE2, TNF-a, IL-1β, IL-6 and the expression of COX-2	Farzaei et al., 2016 Saleem et al., 2019
Althaea rosea Hollyhock Malvaceae	Malvae arboreae flos sine calicibus	Ethanolic extract	Rheumatoid Arthritis	Oil	Anti-inflammatory	Decrease permeability of abdominal capillaries, and reduce paw edema by downregulating the release of PGE from inflammatory tissue	Farzaei et al., 2016
Arctium lappa Garden celery Asteraceae	Bardanae radix Bardanae semen	Infusion Ethanolic extract Butanolic extract	Anti-arthritic Rheumatoid Arthritis	Arctigenin, arctigenin and its glycoside arctin	Anti-arthritic	Up-regulating expression of VEGF and macrophages that unleash inflammatory cytokines and nitric oxide Downregulate interleukins (IL-1β, IL-6, IL-4, IL-5), NO and TNF-α. Suppress the release of iNOS Inhibitor of MAPK	Choudhary et al., 2015, Saleem et al., 2019, Farzaei et al., 2016
Arnica montana Mountain tobacco Asteraceae	Arnicae flos	Extract methanol Extract total	Osteoarthritis, Anti-arthritic	Phenolic and flavonoid compounds	Anti-inflammatory	Decrease in IL-1β, IL-6, IL-12, NO, TNF-α, anti-collagen II antibodies Increase of antioxidants.	Dragoș et al., 2016, Kang et al., 2019 Zang, 2020 Sharma, 2016

Artemisia absinthium Worm-wood Asteraceae	Absinthii herba	Extract	Rheumatoid Arthritis	Scoparone, scopoletin, scopolin, esculetin	Anti-inflammatory	Suppress the release of NO and PGE-2 (proinflammatory compound) Downregulate COX-2, TNF-α, IL-1β, IL-6, and IL-8	Saleem et al., 2019
Betula sp. Birch Betulaceae	Betulae cortex	Extract	Osteoarthritis	Betulin	Anti-inflammatory	Inhibits gene expression of MMP-13, MMP-1, MMP-3 ADAMTS-4, and ADAMTS-5 induced by IL-1β Up-regulate type II collagen's gene expression. Inhibits the secretion of MMP-3 and its proteolytic activity	Kang et al., 2019 Ra et al., 2017
Borago officinalis Starflower Boraginaceae	Boraginis semen	Oil	Rheumatoid Arthritis	Gamma-linoleic acid	Anti-inflammatory	Significant increase in PGE level due to the reduction in cAMP. Suppress the NF-kB, ERK1/2, and JNK1 pathways and TNF-α.	Singh et al., 2020 Ghasemian et al., 2016
Bryonia alba White bryony Cucurbitaceae	Bryoniae radix		Rheumatoid Arthritis	Cucurbitacin glucoside	Anti-inflammatory	Suppress the mediators of inflammation LT-B4 and 5-HETE and adjust corticosteroid secretion	Gautam et al., 2020
Caltha palustris Marsh-marigold Ranunlaceae	Calthae palustridis herba	Extract-methanol Extract	Anti-arthritic	Polysaccharide	Anti-arthritic	Decrease T-regulatory cells ($CD4^+CD25^+FOXP3^-$) Increase NO	Choudhary et al., 2015 Suszko & Obmińska-Mrukowicz, 2017

						synthesis Downregulate IL-1β	
Cannabis sativus Hemp Urticaceae	Cannabis herba et semen	Extract	Anti-arthritic	Cannabin, cannabion, cannabene, cannabinone, and other terpenes	Anti-inflammatory	Inhibits inflammatory mediators Suppression of TNF-α Immunosuppression of a T-helper 1 effector cells response.	Yashika Gandhi et al., 2022
Capsicum annuum Red pepper Solanaceae	Capsici fructus et semen	tincture	Anti-arthritic	Capsaicin	Anti-arthritic	Suppress collagenase, expression from synoviocytes, and the synthesis of PGE2.	Arunsi et al., 2022
Chelidonium majus Great celandine Papaveraceae	Chelidonii herba	Extract methanol	Rheumatoid Arthritis	Chelidonine	Anti-inflammatory	Lower the CD4+ T cells and enhance CD8+ T cells inducing an immunosuppressive response.	Choudhary et al., 2015
Citrullus colocynthis Colocynth Cucurbitaceae	Colocynthidis fructus	Powder (aqueous extract)	Rheumatoid Arthritis	Quercetin	Anti-inflammatory Anti-arthritic	Downregulate IL-6, IL-1β and COX-2 expression; Increases IL-4	Gautam et al., 2020
Clematis vitalba Old man's beard Ranunculaceae	Clematidis herba	Hydroalcoholic extract	Rheumatoid Arthritis	Vitalboside	Anti-inflammatory	Reduce edema and arthritis.	Farzaei et al., 2016
Colchicum autumnale Autumn crocus Colchicaceae	Colchici bulbus et semen	Extract	Rheumatoid Arthritis	Colchicine	Anti-arthritic Anti-inflammatory	Suppress the production of TNF-α, IL-6, and IL-1β and the expression of TNF-R1 in the synovium	Saleem et al., 2019 Choudhary et al., 2015

Coriandrum sativum Coriander Apiaceae	Coriandri fructus	Oil hydroalcoholic extract from seed, stem, and leaves	Anti-arthritic	γ-Linolenic acid Cineole	Anti-inflammatory Anti-arthritic	Downregulate IL-6, IL-1B and TNF-α, TNF-R1	Yashika Gandhi et al., 2022 Singh et al., 2020 Gautam et al. 2020
Crocus sativus Saffron Iridaceae	Croci stigma	Tincture, infusion Extract	anti-arthritic Osteoarthritis	Crocin, Crocetin, Safranal	Anti-inflammatory, Anti-arthritic	Suppress the NF-κB signaling pathway in joint chondrocytes blocking the expression of MMP-13, MMP-3, and MMP-11 Reduce degeneration of cartilage.	Choudhary et al., 2015 Kang et al., 2019 Tsiogkas et al., 2021
Cymbopogon citratus Citronella Poaceae	Cymbopogonis citrati herba	Oil	Rheumatoid Arthritis	geraniol, neral, limonene, citral	Anti-arthritic	Activate PPARα and γ; Inhibition of COX-2, NO production, Suppress expression of iNOS, DNA-binding activity, and nuclear translocation of NF-κB and IκB kinase phosphorylation	Arunsi et al., 2022
Cuscuta campestris Field dodder Convolvulaceae	Cuscutae semen	Extract metanolic	Rheumatoid Arthritis	Quercetin	Anti-inflammatory	Reducing NO	Farzaei et al., 2016
Cuscuta epithymum Dodder Convolvulaceae	Cuscutae semen	Extract metanolic	Rheumatoid Arthritis	Quercetin	Anti-inflammatory	Mediate the suppression of NF-κB expression through the downregulation of cytokines, COX-2 and TNF-α.	Saleem et al., 2019

Elaeagnus angustifolia Oleaster Elaeagnaceae	Elaeagni fructus	aqueous and ethanol extracts	Osteoarthritis	Kaemferol	Analgesic Anti-inflammatory	Inhibits COX-1 and COX-2 Downregulate TNF-α and IL-6, mediators (NO and PGE2) Signaling kinases (Src, Syk, and IRAK4), and release of ROS.	Panahi et al., 2016
Ephedra sinica, *Ephedra spp.* Chinese ephedra Ephedraceae	Ephedrae herba	Aqueous extract	Rheumatoid Arthritis Anti-arthritic	Polysaccharides, Ephedrine alkaloids	Anti-inflammatory, immunosuppressive, analgesic Anti-arthritic	Suppress the TLR4 signaling pathway and reduce NF-κB, downregulating the release of inflammatory factors and cytokines. Regulate the expressions of TNF-α and IL-6 genes.	Xia et al., 2020 Choudhary et al., 2015
Equisetum arvense Horsetail Equisetaceae	Equiseti herba	Extract	Osteoarthritis Rheumatoid Arthritis	Kynurenic acid	Anti-inflammatory, anti-oxidative, and pain-relieving properties	Reduce synoviocyte proliferation Downregulate the level of TNF-α and IL-10.	Dragoş et al., 2017 Jiang, 2014
Fraxinus excelsior European ash Oleaceae	Fraxini folium	Decoction of dried leaves	Anti-arthritic	flavonoids: rutoside, quercitroside, phenolic acids: caffeic acid, coumarin derivatives: esculoside, fraxoside, secoiridoids: excelsioside, oleuropein, ligstroside, mucilage.	Anti-inflammatory	Inhibition of xanthine oxidase	Villeneuve, 2017

Glycyrrhiza glabra Liquorice Fabaceae	Liquiritiae radix	Extract methanol Extract	OsteoArthritis, Anti-arthritic	Flavonoids Licochalcone A Glycyrrhetinic acid Liquiritin, glycyrol, glycyrrhizin Prunetin	Anti-inflammatory	Suppresses bone and cartilage erosion. Suppresses the expression of IL-1β, IL-18 and NLRP3 Inhibits COX-2, production of MMP-3 stimulated by IL-1β	Choudhary et al., 2015 Yashika Gandhi et al., 2022 Xia et al., 2020 Singh et al., 2020 Kang et al., 2019
Hedera helix English ivy Araliaceae	Hederae helicis folium	Extract ethanol	Rheumatoid Arthritis/injection	Saponin	Anti-inflammatory	Reduction in arthritic symptoms	Choudhary et al., 2015 Rai, 2013
Humulus lupulus Hop Cannabaceae	Lupuli strobuli, Lupuli glandulae	Infusion		humulone	Anti-arthritic	Suppress COX-2 gene transcription Inhibition of PGE_2 production	Choudhary et al., 2015 Hougee et al., 2006
Inula helenium Elecampane Asteraceae	Inulae rhizoma et radix	Extract	Rheumatoid Arthritis	Dihydroflavonols Sesquiterpene lactones, mainly alantolactone, isoalantolactone	Anti-inflammatory	Inhibition of TNF-α, MCP1, MCP2, MMP3, IL-1, IL-6	Midhun Kumar et al., 2020 Singh et al., 2020
Linum usitatissimum Flaxseed Linaceae	Lini semen	Petroleum ether	Anti-arthritic	alpha linolenic acid	Anti-arthritic	Inhibition of arachidonate metabolism through suppressing the production of n-6 eicosanoids PGE2, LTB4, and diminishing vascular permeability	Choudhary et al., 2015 Kaithwas et al., 2010
Lonicera japonica Japanese honeysuckle Caprifoliaceae	Lonicerae folium	Extract methanol	Anti-arthritic	Luteolina	Anti-inflammatory	Suppress T-cell proliferation	Choudhary et al., 2015

Matricaria chamomilla Camomile Asteraceae	Chamomillae flos	Oil Tea	Osteoarthritis Rheumatoid Arthritis	apigenin, quercetin, patuletin,luteolin and glucozide	Anti-arthritic Anti-inflammatory	Reduction in need for acetaminophen. Reducing cytokines and PGE2	Lindler et al., 2020
Nigella sativa Black cumin Ranunculaceae	Nigellae semen	Aqueous extract Extract	Anti-arthritic, Rheumatoid Arthritis	Thymoquinone	Anti-inflammatory Anti-arthritic	Reduce TLR2, TLR4, TNF-α, NFκB, the levels of COX-2, IL-1 β, IL-6, IL-8, IL-12, and IL-16.	Arjumand et al., 2019 Yashika Gandhi et al., 2022 Saleem et al., 2019
Ocimum basilicum Basil Lamiaceae	Basilici herba	Extract	Rheumatoid Arthritis	Rutin (Vitamin P)	Anti-arthritic	Inhibition in oxidative stress markers of NO, T cells proliferation and $NADP^+$ oxidase. Reduce edema, cartilage and bone erosion. Up-regulation of SOD, GPx, and GSH, downregulation of MDA levels. Inhibition of TNF-α, IL-1β, and NF-κB.	Arunsi et al., 2022
Oenothera biennis Evening primrose Onagraceae	Oenotherae semen	Extract	Rheumatoid Arthritis	GLA-gamma-linoleic acid	Anti-inflammatory	Modulation of nitric oxide (NO), TNF-α, IL-1β and TXB2 resulting in suppressing of COX-2	Singh et al., 2020

Osmunda regalis Royal fern Osmundaceae	Osmundae herba	Extract	-	-	Anti-arthritic	-	Choudhary et al., 2015
Peganum harmala Wild rue Zygophyllaceae	Pegani harmalae folium seeds	Decoction Peganum oil	Rheumatoid Arthritis	Alkaloids	Anti-arthritic Analgesic	Reducing pain and difficulty in function	Choudhary et al., 2015 Abolhassanzadeh et al., 2015
Phellodendron amurense Amur cork tree Rutaceae	bark	Extract ethanol	Osteoarthritis	Palmatine, protoberberin	Anti-inflammatory Analgesic	Suppress IL-1β-stimulated type II collagen degradation and release of proteoglycans leading to cartilage protection.	Kang et al., 2019
Physalis alkekengi Strawberry tomato Solanaceae	*Alkekengi* fructus	Extract Aqueous	Anti-arthritic	Polyphenols Physalins, sophysalin B, and aromaphysalin B	Anti-arthritic, anti-inflammatory	Inhibits protein denaturation Reduce NO production; Suppress TNF-α, IL-6 and IL-12	Choudhary et al., 2015 Yang Y. et al., 2022
Pinus cembra Swiss stone pine Pinaceae	Pinis cembra propolis	Extract	Osteoarthritis	Pinocembrin (flavonoid)	Protective effect	Inhibits MMP-1, MMP-13, and MMP-3 expression by modulating the NF-κB signaling pathway	Kang et al., 2019 Zhang et al., 2015
Plantago major Broadleaf plantain Plantaginaceae	Plantaginis folium	Extract	Anti-arthritic	n-hexane-insoluble fraction of dichloromethane extracts	Anti-arthritic	Decrease expression of TNF-α and IL-6.	Choudhary et al., 2015 Triastuti et al., 2021
Populus nigra L. Black poplar Salicaceae	Populi gemma	Extract	Anti-arthritic	Flavonoids	Anti-inflammatory	Adjust the production of TNF-α, IL-1β, IL-6, IL-10	Oroian, 2011 Kis et al., 2020 Oroian et al., 2019
Portulaca oleracea Common purslane, Pursley Portulacaceae	Portulace folium	Petroleum ether extract Juice, poultice	Anti-arthritic	alkaloids, tannins, flavonoids, saponins, and triterpenoids	Anti-inflammatory Anti-arthritic	Downregulate IL-1, IL-6, and TNF-α	Jaya Sankar Reddy et al., 2014 Choudhary et al., 2015 Nadipelly et al., 2012

							Allahmoradi et al., 2018
Ranunculus sceleratus Celery-leaved buttercup Ranunculaceae	Ranunculi sceleratus herba	Extract	Rheumatoid Arthritis	myristic acid, Phytol, B-sitosterol, Stigmasterol, Ranunculin	Anti-inflammatory	Suppress production of eicosanoid, PLA2, and 12-LOX pathway	Gautam et al., 2020
Reynoutria japonica Japanese knotweed Polygonaceae	Reynoutriae radix	Extract	Osteoarthritis	Resveratrol	Anti-inflammatory	Block the NF-κB signaling pathway leading to suppression of iNOS, COX-2, TNF-α, and IL-1β expression; Inhibits the MMP-3 gene expression and secretion	Kang et al., 2019 Cucu et al., 2021 Dursus, 2018 Nawrot-Hadzik et al., 2021
Rheum palmatum Chinese rhubarb Polygonaceae	Rhei rhizoma	Extract	Rheumatoid Arthritis	Emodin	Anti-inflammatory,	Regulate TNF-α, iNOS, and IL-10, IL-6, IL-8, PGE2, MMP-1, COX-2, VEGF as well as NF-jB	Farzaei et al., 2016 Saleem et al., 2019
Ribes nigrum Blackcurrant Grossulariaceae	Ribes nigri muguri	Extract	Rheumatoid Arthritis	α-linolenic acid Flavonoids Proanthocyanidins Phenolic acids Vitamin C	Anti-inflammatory, analgesic; anti-arthritic	inhibiting the expression of IL-6 and TNF-α iNOS, and IL-10 as well as NF-jBp65	Musco et al., 2019 Villeneuve, 2017
Ricinus communis Castor Oil Euphorbiaceae	Ricini semen	Oil, poultice	Rheumatoid Arthritis	Polyphenols and flavonoids	Anti-inflammatory	Suppress IL-1β, IL-6, IL-17a, TNF-α, and RANKL Modulation of IL-4, INF-gamma, and OPG expression	Choudhary et al., 2015

Ruta graveolens Common rue Rutaceae	Rutae herba	Extract	Anti-arthritic	Polyphenols	Anti-inflammatory	Down-regulate TBARS, COX-2, 5-LOX and MPO level Reduce NO, TNF-α, IL-1β, and IL-6	Choudhary et al., 2015 Sahu et al., 2015
Salix alba White willow Salicaceae	Salicis cortex	Decoction Aqueous Extract	Osteoarthritis and Rheumatoid Arthritis	salicin, polyphenols, flavonoids	Anti-arthritic anti-inflammatory	Inhibit translocation of the transcription factor NF-κB Regulate COX-1, COX-2, 5-lipoxygenase (5-LOX), TNF-α, IL-1, IL-6, and NO	Dragoș et al., 2017 Bonatera et al., 2010 Henrotin, Y., & Mobasheri (2018)
Saussurea lappa Costus Asteraceae	Costus radix	Extract	Anti-arthritic	Cynaropicrin Dehydrocostus	Anti-inflammatory anti-arthritic	Inhibits production of TNF- α Supresses the production of LPS-induced NO	Yashika Gandhi et al., 2022
Sesamum indicum Sesame Pedaliaceae	Sesami oleum	Oil	OsteoArthritis and Rheumatoid Arthritis	sesamin, sesamol,sesamolin	Anti-arthritic, anti-inflammatory	Regulate TNF- α, IL-1β, IL-6, COX-2, MMP-13, MMP-3, MMP-9 gene expression	Dragoș et al., 2017 Askari, et al., 2019
Solanum melongena Eggplant Solanaceae	Solani melongena fructus	Extract	Rheumatoid Arthritis	Apigenin	Anti-inflammatory	Decreases the level of TNF-α, IL-1β, and IL-6 Inhibits CXCR4 gene expression.	Arunsi et al., 2022
Solanum nigrum Black nightshade Solanaceae	Solani nigri folium	poultice		Solanine A	Anti-arthritic	Suppresses TNF-α, IL-1β, and IL-6 and NF-κB	Choudhary et al., 2015 Zhao et al., 2018
Symphytum officinale Comfrey Boraginaceae	Symphyti radix	Extract hydroalcoholic extract	OsteoArthritis and Rheumatoid Arthritis	rosmarinic acids, glycopeptides, amino acids	Anti-inflammatory, analgesic	Regulate pain and articular mobility Suppresses activation of NF-κB Regulate IL-1, and COX-2	Dragoș et al., 2017 Kang et al., 2019 Seigner et al., 2019

Thymus vulgaris Garden thyme Lamiaceae	Thymi herba	Oil	Anti-arthritic	Carvacrol (monoterpene phenol)	Anti-inflammatory	reduce TNF-α IL- 8 and IL−6 inhibit MMP- 1, MMP- 3, and MMP- 13suppresses activation of NF- κB	El-Sheikh et al., 2019
Tribulus terrestris Land-Caltrops Zygophyllaceae	Tribuli terrestris fructus	methanolic extract	Anti-arthritic	N -trans- p -caffeoy l tyramine Tribulusamide D	Anti-inflammatory	Modulate COX-2, TNF-α, IL-6, and NO synthase 2 Inhibits MMP-2 and MMP-9 expression	Choudhary et al., 2015 Yashika Gandhi et al., 2022 Jaya Sankar Reddy et al., 2014 Park et al., 2017
Urtica dioica Common nettle Urticaceae	Urticae folium	Extract hydroalcoholic extract	Osteoarthritis and Rheumatoid Arthritis	Carvacrol, carvone, chlorogenic acid, phaselic acid, rutin Neophytadiene, Phtaleic acid, Dibutyl phthalate, Bis (2-ethyl hexyls') maleate, 1,2-benzenocli carboxylic acid	Anti-inflammatory	Inhibits NF-κB and AP-1 activation Block cytokines expression and eicosanoids formation Suppresses expression of (MMPs)-9 and 3	Gautam et al., 2020 Anvari et al., 2022 Goswami et al., 2022 Villeneuve, 2017
Vitis sp. Grapevine Vitaceae	Vitis viniferae semen	Extract	Osteoarthritis	Proanthocyanidins	Antioxidant Anti-inflammatory	Inhibits NO, PGE2, TNF-α IL-1β, and IL-17	Anvari et al., 2022
Xanthium strumarium Common cocklebur Asteraceae	Xanthii herba	Ethanol extact	anti-arthritic	alkaloids	Anti-inflammatory	Downregulate TNF-α, IL-1β; COX-2 and 5-LOX. Increase IL-10.	Choudhary et al., 2015 Lin et al., 2014

Abbreviations: IL-1β: interleukin 1 beta; IL-4: interleukin 4; IL-5: interleukin 5; TNF-α: tumor necrosis factor-alpha; TNF-R1: Tumor necrosis factor receptor 1; E-NTPDase: ecto-nucleoside triphosphate diphosphohydrolase; IFN-gamma: Interferon-gamma; CRP: c-reactive protein; COX-2: cyclooxygenase-2; PGE2: prostaglandin E2; VEGF: vascular endothelial growth factor; iNOS: inducible nitric oxide synthase; MAPK: mitogen-activated protein kinase; NO: nitric oxide; cAMP: cyclic adenosine monophosphate; NF-κB: Nuclear factor kappa B; LTB4: Leukotriene B4; 5-HETE: 5-Hydroxyeicosatetraenoic acid; IkB: inhibitor of nuclear factor; Src: Human Recombinant Protein, Syk: Tyrosine-protein kinase); IRAK-4: interleukin-1 receptor-associated kinase 4; ROS: reactive oxygen species; NLRP3: NLR family pyrin domain containing 3; MCP1, 2: Monocyte chemoattractant protein-1, 2; NADP+: Nicotinamide adenine dinucleotide phosphate; TXB2: thromboxane B2; PLA2: phospholipase A_2; 12-LOX: 12-Lipoxygenase; NF-jB: Stimulus-induced nuclear factor-jB; RANKL: Receptor activator of nuclear factor kappa-B ligand; OPG: Osteoprotegerin; TBARS: Thiobarbituric acid reactive substances; AP-1: activator protein 1; MMP: Matrix metallopeptidase.