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Flavonoids, alkaloids and saponins: are these plant-derived compounds an alternative to the treatment of rheumatoid arthritis? A literature review

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Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by synovial inflammation leading to progressive joint erosion and, eventually, joint deformities. RA treatment includes anti-inflammatories, corticosteroids, synthetic disease-modifying antirheumatic drugs (DMARDs), and immunosuppressants. Drug administration is associated with adverse reactions, as gastrointestinal ulcers, cardiovascular complications, and opportunistic infections. Wherefore, different plant-derived phytochemical compounds are studied like new therapeutic approach to treatment of RA. Among the phytochemical compounds of plants for treatment of RA, flavonoids, alkaloids and saponins are related for present anti-inflammatory activity and act as physiological and metabolic regulators. They have low toxicity compared to other active plant compounds, so their therapeutic properties are widely studied. The intention of the review is to present an overview of the therapeutics of flavonoids, alkaloids, and saponins for RA. An extensive literature survey was undertaken through different online platforms:
PubMed, SciELO, and Virtual Health Library databases, to identify phytochemical compounds used in RA treatment and the descriptors used were medicinal plants, herbal medicines, and rheumatoid arthritis. Seventy-five research and review articles were found to be apt for inclusion into the review. The present study summarizes the phytochemicals isolated from plants that have therapeutic effects on RA models, *in vitro* and *in vivo*. The studied substances exerted anti-inflammatory, chondroprotective, immunoregulatory, anti-angiogenic, and antioxidant activities and the most compounds possess good therapeutic properties, valuable for further research for treatment of RA.

Keywords: Phytochemical compounds, Flavonoids, Alkaloids, Saponins, Articular disease

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Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by symmetrical arthritis and synovial inflammation, progressive joint erosion, and, eventually, joint deformities. It presents autoimmune features and unknown etiology [1, 2]. The treatment includes anti-inflammatories, corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and immunosuppressive drugs [3]. Therapeutic drugs used to RA treatment induce many adverse effects such as dermatologic disorders (oral ulcers, alopecia, rash, anaphylactic reactions, photosensitivity, vasculitis and nodulosis), gastrointestinal disturbances (nausea, vomiting, diarrhoea, gastrointestinal bleeding, complication of ulcers), hepatic disease (elevation of liver enzymes, mild and severe fibrosis, cirrhosis), nervous disorders (headache, dizziness, vertigo, fatigue, mood alteration, memory impairment), besides immunosuppression (opportunist infections), serositis (cardiovascular system), osteopathy and renal insufficiency. Due to large number of side effects the use of therapeutic drugs is not always fully effective in RA treatment [3–5].

Phytotherapies that are approved for clinical treatments, which motivates the search for other substances with therapeutic potential for RA, including phytochemicals present in plants [5–7]. Among the phytochemical compounds present in plants, flavonoids, alkaloids and saponins are most related for treatment of RA. They have low toxicity, and their therapeutic properties are widely studied. They are commonly known for their antioxidant properties but have anti-inflammatory effects, inhibiting pro-inflammatory cytokines, pro-apoptotic effects through the production of caspases, inhibits cartilage and bone destruction, and angiogenesis [8–11]. Flavonoids present antioxidant, anti-inflammatory, and immunomodulatory activities [12]. Alkaloids have mainly immunomodulatory action, regulating the cytokines IL-6, IL-12, IL-1α, TNF-α, IL-1β, and IL-10 [13]. Similarly, saponins also have immunostimulatory properties in RA, mainly in fibroblast-like synoviocytes [14–16].

Thus, the present compilation aimed to highlight an overview of the therapeutic properties of flavonoids, alkaloids, and saponins as potential therapeutic agents for RA.

Methodology

Substantial literature survey was undertaken to abridge the phytochemical compounds in the treatment of rheumatoid arthritis and its therapeutic properties. We performed a literature review in PubMed, SciELO, and Virtual Health Library databases, to identify medicinal plants used in RA treatment. The descriptors used were medicinal plants, herbal medicines, and rheumatoid arthritis. The acceptability criteria of the included studies were publications about compound phytochemicals isolated from plants that have therapeutic effects on RA models, *in vitro* and *in vivo*.

Immunopathology of rheumatoid arthritis

Although the etiology of RA is not clarified, it is possible to affirm that the disease results from the action of autoreactive T and B cells. The cells originate a synovitis process, cell infiltration, bone destruction, and remodeling. Osteoclasts and osteoblast mediate both bone destruction and the remodeling process. During bone erosion, there is an increase in the production of the receptor activator of nuclear factor-kappa-B ligand (RANK L), IL-1, and macrophage colony-stimulating factor (M-CSF). Bone damage also occurs through the action of matrix metalloproteinases produced by macrophages, such as MMP9 [17, 18].

T cells have a role in the pathogenesis of RA, especially Th17 cells. Th17 cells enhance the production of inflammatory cytokines (IL-6, IL-1β, and TNF-α), coordinate bone and cartilage damage [2, 19]. Liu et al. [13] report that high concentrations of TNF-α, IL-17, and IL-6 are found in collagen-induced arthritis rats, representing the starting point for the inflammatory and immunological process of RA [20, 21]. It is important to highlight that the inflammatory process in RA involves several cells, including macrophages, fibroblasts, synoviocytes, lymphocytes, chondrocytes, osteocytes, among others [2].

Clinical studies consolidated and validated the major contribution of cytokines to RA pathogenesis [22]. A variety of cytokines appear before the onset of joint disease and throughout the transition from systemic to local disorder [23]. Cytokines are typically secreted by leukocytes and released in the synovial membrane and joint space. Several cytokines of the adaptative immune response are part of the inflammatory process. The joints affected by RA present cell infiltrates composed of $CD4^+$ and $CD8^+$ T cells, lymphoblasts, plasmocytes, macrophages, and neutrophils, besides pro and anti-inflammatory cytokines and chemokines [22–24] .

Prostaglandins and leukotrienes are produced in response to physiological or pathological stimuli, such as synovial membrane injury caused by RA [22]. When the inflammatory process is installed, neutrophils and $CD4^+$ T cells release enzymes, which causes damage to the joint structure [23]. There are three subtypes of T helper lymphocytes, according to the pattern of cytokines they produce. The antigen is presented to naïve T cells in secondary lymphoid organs, which can differentiate into Th1, Th2, or Th17 cells [25]. The cytokines IL-12 and IFN-γ activate Th1 cells, IL-4, IL-5, and IL-13 activate Th2 cells, and TGF-β and IL-6

activate Th17 cells [22, 23, 25]. The main cytokines involved in this process are listed in Table 1.

Phytochemical compounds in the treatment of rheumatoid arthritis

The number of patients with rheumatoid arthritis increases each year. However, the medications used in the treatment have many side effects. Therefore, there is an intense search for alternative therapies, cheaper, effective, and with fewer side effects [26]. Herbal medicines stand out for their curative effects, and many of them are used for RA clinical treatment [27, 28]. But their efficacy and safety in a long-term clinical application need to be discussed [29, 30].

Medicinal plants and their secondary metabolites act in various ways in RA prevention and treatment. Among the components, we highlight the pharmacological effects of flavonoids, alkaloids, and saponins. The effects are related to pain relief, regulation of immune response, cartilage protection, inhibition of synovial hyperplasia, and others [30, 31].

Flavonoids

There are more than 6,000 flavonoids that act as physiological and metabolic regulators in plants. They present broad action and relatively low toxicity compared to other active plant compounds [12].

Flavonoids are synthesized by the phenylpropanoid metabolic pathway. Along this pathway, flavonoid subgroups with different structural patterns are formed. These structural variations explain the differences observed in the bioactivity of these compounds to the organism [32, 33].

Flavonoids are commonly known for their antioxidant properties; however, they can also exert anti-inflammatory effects. They inhibit the production of pro-inflammatory cytokines, nitric oxide (NO), eicosanoids, and interfere with the NF-kB transcription factor [34–37]. The Table 2 describes studies that used flavonoids for RA treatment.

Quercetin is a flavonoid with remarkable properties against RA. When administered orally in rats with collagen-induced arthritis (150 mg/mL), it decreased the production of IL-17 A and IL-21 [11]. In RAW 264.7 and HIG-82 cells, it decreased TNF-α levels [8]. In a double-blind, randomized controlled trial with 50 women, treated with 500 mg/day for eight weeks, quercetin reduced pain and TNF-α levels [58]. Hesperidin showed protective activity against RA in Wistar rats at a concentration of 50 mg/kg. There was a significant reduction of joint destruction and serum levels of TNF-α when compared to control [59].

The flavonoids baicalin and aglycone (baicalin-2) are found in large amounts in the medicinal plants *Scutellaria baicalensis* and *Oroxylum indicum*. They have anti-inflammatory and antioxidant activity due to the reduction in reactive oxygen species (ROS) generation, attenuation of NF-kB activity, reduction of cyclooxygenases and TNF-αtumor necrosis factor. For this reason, they are potential targets for RA treatment [9].

Flavonoids from *Daphne genkwa*, as follows: gentakwanin, hydroxygenkwanin, luteolin, and apigenin, demonstrated anti-inflammatory and immunomodulatory activity. They reduced the expression NO, ROS, TNF-α, IL-6, IFN-γ, and IL-2, which is effective for combating RA [60, 61].

Table 1 Cytokines and their role in the immunopathogenesis of Rheumatoid Arthritis

Cytokine	Producer cells	Target Cell and Effect	Role in Rheumatoid Arthritis	Reference
TNF-α	Monocytes/ Macrophages.	Pro-inflammatory action. Differentiation and activation of osteoclasts. Neovascularization of the endothelium. Inhibition of regulatory T lymphocytes.	Systemic bone erosion	[24]
IL-6	Monocytes/ Macrophages.	Macrophage activation and proliferation, with differentiation into osteoclasts. Multiplication and differentiation of T lymphocytes in the Th17 subtype.	Systemic inflammation	[25]
IL-1α/b	Monocytes/ Macrophages.	Osteoclast activation. T lymphocytes differentiation. Vasodilation.	Pro-inflammatory	[26]
IL-17 A	Th17 lymphocytes/ neutrophils	Cell proliferation. IL-6 production. Chondrocyte multiplication. Myeloid cells and neutrophil chemotaxis. Endothelial neovascularization.	Pro-inflammatory	[27, 28]
IL-23	Macrophages	Development, maintenance, and expansion of Th17 lymphocytes. Induction of IL-21/IL-22 cytokine production.	Th17 lymphocytes	[29]
IL-21	Th17 lymphocytes/Th2 cells/NK cells	B cell maturation. Development of plasma cells and production of antibodies.	Glycosylation of arthritogenic autoantibodies	[30]
IL-12	Macrophages	Differentiation of Th1 lymphocytes	Cell-mediated immune responses, Th17 cell plasticity	[31]

Table 2 Phytochemicals used in the treatment of rheumatoid arthritis

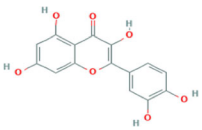
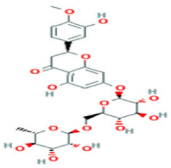
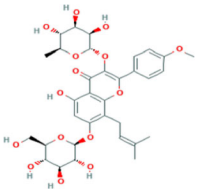
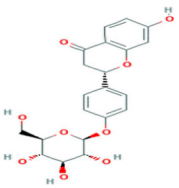
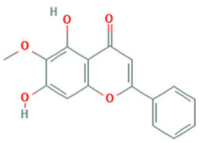
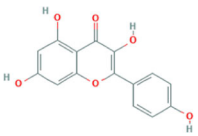
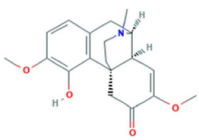
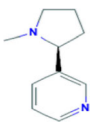
Compound	Chemical structure	Mechanism of action	Effect	References
Flavonoids				
Quercetin		Decreased expression of IL-17 A, IL-21, and TNF-α. Decreased migration of Th17 lymphocytes. Increased expression of IL-10.	Decreased morning pain. Anti-inflammatory activity.	[6–8, 38]
Hesperidin		Decreased expression of TNF-α. Decreased osteoclastogenesis.	Anti-inflammatory activity. Decreased destruction of joint cartilage.	[39]
Baicalin Aglycone	**	Decreased ROS and cyclooxygenase production. Decreased activation of the NFkB signaling pathway.	Anti-inflammatory and antioxidant activity.	[9]
Gentakwanin Hydroxygenkwanin Luteolin Apigenin	**	Decreased NO and ROS production. Decreased production of TNF-α, IL-6, INF-γ, and IL-2.	Anti-inflammatory, immunomodulatory, and antioxidant activity.	[40, 41]
Icariin		Decrease in osteoclastogenesis markers. Decrease in Th17 lymphocyte population.	Decreased destruction of bones and cartilage. Anti-inflammatory activity.	[42]
Liquiritin		Decreased BCL-2/BAX rate. JNKI/P38 phosphorylation.	Anti-inflammatory activity. Angiogenic activity.	[43]
Oroxylin A		Decreased rates of IL-1β, IL-6, TNF-γ, and IL-17.	Anti-inflammatory activity	[44]
Kaempferol		Decreased invasion, proliferation, and invasion of fibroblast-like synoviocytes. Decreased production of TNF-α.	Anti-inflammatory activity. Reduction of cellular infiltrate.	[45, 46]
Alkaloids				
Sinomenine		Regulation of IL-6, IL-12, INF-γ, TNF-α, IL-1β, and Il-10.	Anti-inflammatory activity.	[13, 47, 48]
Nicotine		Decreased rates of rheumatoid factor, C-reactive protein, NO, and myeloperoxidase. Reduced levels of IL-1 and IL-17.	Anti-inflammatory activity	[49]

Table 2 Phytochemicals used in the treatment of rheumatoid arthritis *(Continued)*

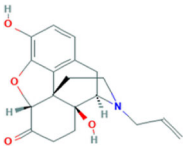
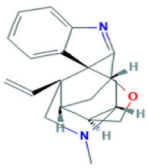
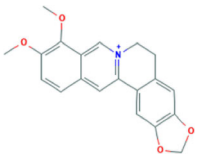
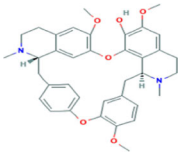
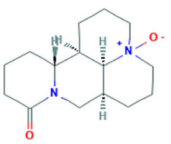
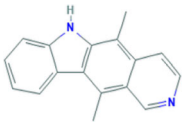
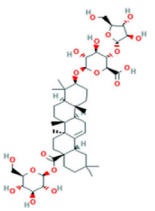
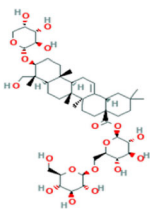
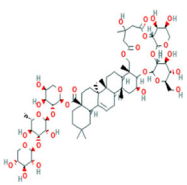
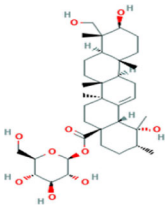
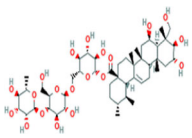
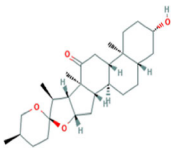
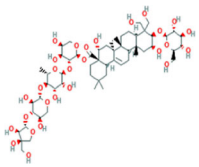
Compound	Chemical structure	Mechanism of action	Effect	References
Naloxone		Not specified.	Decreased joint pressure.	[50]
Koumine		Immunomodulation.	Attenuating RA progression.	[51]
Berberine		Decreased production of IL-6 and IL-17. Increased production of IL-10 and TGF-β.	Reduces synovial hyperplasia. Anti-inflammatory activity.	[52]
Fangchinoline		Decreased production of TNF-α, IL-6, NO, uric acid, and cerulopasmin. Decreased proliferation of chondrocytes.	Anti-inflammatory activity. Reduction of cartilage degradation.	[53]
Oxymatrine		Decreased production of IL-6 and IL-8. Decreased migration and invasion of fibroblast-like synoviocytes. Activation of the NFkB signaling pathway. Decreased Th17 lymphocyte population. Increased regulatory T lymphocyte population.	Anti-inflammatory activity.	[54]
Ellipticine		Inhibition of fibroblast-like synoviocytes proliferation. Induction of apoptosis.	Anti-inflammatory and pro-apoptotic activity.	[55]
Saponins				
Araloside A		Decreased proliferation of fibroblast-like synoviocytes. Induction of apoptosis. Decreased production of IL-6, IL-8, Prostaglandin E2, and NO. Activation of NFkB signaling pathway.	Anti-inflammatory and pro-apoptotic activity.	[10]
Asperosaponin VI		Inhibits osteoclastogenesis, by inducing the expression of several genes and markers that lead to osteoclast proliferation.	Decreased bone destruction.	[15]
Tubeimoside I		Decreased production of IL-1β, IL-6, IL-8, and TNF-α. Decreased expression of MMP9. Attenuation of fibroblast-like synoviocytes phenotypes.	Anti-inflammatory activity.	[16]

Table 2 Phytochemicals used in the treatment of rheumatoid arthritis *(Continued)*

Compound	Chemical structure	Mechanism of action	Effect	References
Pedunculoside		Decreased migration and activation of fibroblast-like synoviocytes. Decreased production of IL-1β, IL-6, IL-8, and TNF-α. Activation of p38 protein.	Anti-inflammatory and pro-apoptotic activity.	[56]
Medecassoside		Decreased migration and invasion of fibroblast-like synoviocytes. Decreased production of IL-1β. Activation of NFkB signaling pathway.	Anti-inflammatory and pro-apoptotic activity.	[57]
Hecogenin		Decreased migration and invasion of fibroblast-like synoviocytes. Induces apoptosis by increasing caspases 3, 8, and 9.	Anti-inflammatory and pro-apoptotic activity.	
Platycodin D		Decreased production of IL-6 and TNF-α.	Anti-inflammatory activity.	

*All chemical structures of the described compounds were obtained on PubChem platform, of the National Library of Medicine (available at: https://pubchem.ncbi.nlm.nih.gov)
**Chemical structure formed by more than one phytochemical compound

Icariin, a natural flavonoid isolated from plants of the Epimedium family, decreased bone and cartilage degradation in mice with collagen-induced arthritis. It also inhibited osteoclastogenesis markers in vitro, such as β3 integrin, cathepsin K, and MMP9, in addition to decreasing the number of Th17 cells [62].

Liquiritin, a flavonoid extracted from the roots of *Glycyrrhiza uralensis*, induces synovial membrane apoptosis, promotes DNA fragmentation, changes in the mitochondrial membrane, and decreases the BCL-2/BAX rate, resulting in the reduction of inflammation in collagen-induced arthritis in Wistar rats [63].

Another active compound against RA is oroxylin A, a flavonoid known for its anti-inflammatory properties. In an induced RA model in mice, animals treated with oroxylin A (10 mg/mL) presented reduced serum levels of IL-1β, IL-6, TNF-α, and IL-17. Analysis of the T cell population showed an increased number of regulatory T cells, demonstrating a significant anti-inflammatory activity [38].

Kaempferol inhibits the migration, invasion, and proliferation of fibroblast-like synoviocytes (essential cells in the process of cartilage destruction) and decreases the expression of TNF-α. It has a considerable activity against RA, decreasing synovial inflammation and reducing cellular infiltrate [14, 39]. The roles of flavonoids are summarized in Fig. 1.

Alkaloids

Alkaloids are a heterogeneous group derived from amino acids with varied biological activities [40, 41] and can be produced by various organisms, such as bacteria, fungi and plants. Here, we will describe studies that used alkaloids in RA treatment. The main points are in Table 2.

Sinomenime is an alkaloid approved by the Chinese government for RA treatment. It is an anti-inflammatory that regulates the expression of IL-6, IL-12, IL-1α, TNF-α, IL-1β, and IL-10, being a cost-effective alternative to RA treatment [13]. It is also effective when combined with methotrexate, at a dose of 120 mg/day (3:2 proportion). A double-blind study, with 120 patients observed for 24 weeks, demonstrated that the combination resulted in a significant reduction of gastrointestinal side effects [42]. Moreover, sinomenine showed satisfactory results when used through an antioxidant surface thansethosome combined with ascorbic acid, acting on the joint for anti-inflammatory purposes [43].

Nicotine is another active compound in RA treatment. Golbahari and Froushani [44] studied the anti-inflammatory effect of nicotine and thymol in Wistar rats with collagen-induced RA. The animals were treated with nicotine orally (2.5 mg/kg) and showed a significant reduction in the severity of the pathology, as well as decreased rheumatoid factor markers, such as C-reactive

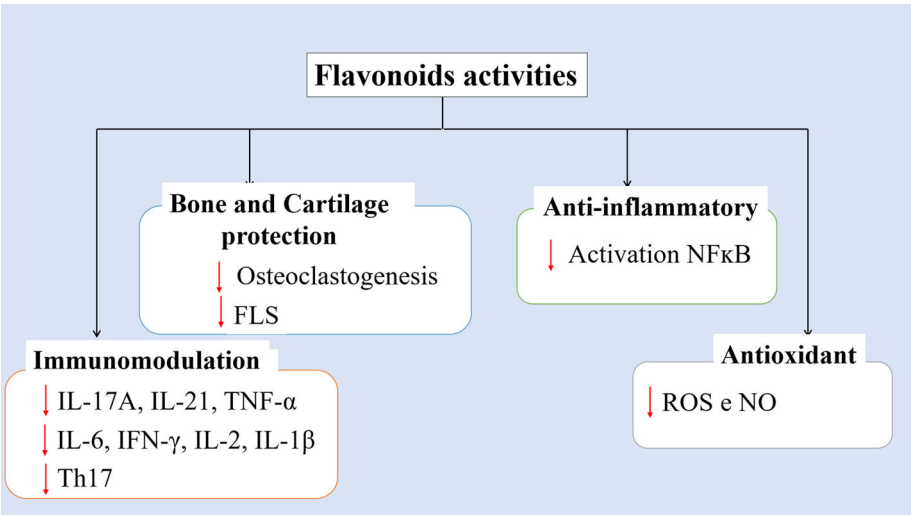


Fig. 1 Biological activities of flavonoids in RA. Legends: FLS- fibroblast-like synoviocytes, NFkB - nuclear factor κB, IL- interleukin, IFN - interferon, TNF - tumor necrosis factor, ROS - reactive oxygen species and NO - nitric oxide

protein, NO, myeloperoxidase, IL- 1, and IL-17. Nicotine, alone or combined with thymol, improved the inflammatory process.

Naloxone is a synthetic alkaloid used as an opioid antagonist. In a double-blind study, patients with RA received a combination of naloxone (0.2 mg/mL) and morphine (10 mg/mL) and had a significant decrease in joint pressure [45].

Yang et al. [46] studied the effects of koumine, an alkaloid from *Gelsemium elegans*, in two experimental RA models in rats, adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA). Koumine significantly inhibited RA progression in both models.

Another compound that acts as an adjuvant is berberine. It reduced RA severity in Wistar rats, decreasing IL-6 and IL-17 production and increasing the expression of IL-10 and TGF-β. Moreover, it attenuates synovial hyperplasia and decreases the inflammatory infiltrate in the joint [64].

Fangchinoline significantly reduces the levels of IFN-α, IL-6, NO, uric acid and ceruloplasmin, when used in the treatment of rats with collagen-induced RA. It induces chondrocyte proliferation, thus reducing cartilage degeneration [65].

Oxymatrine reduces the expression of IL-6 and IL-8, the migration and invasion of fibroblast-like synoviocytes, and activates the NF-kB signaling pathway. It is potent for joint protection due to its anti-inflammatory response [47]. Ma et al. [48] demonstrated that oxymatrine has the ability to regulate lymphocytes cellular response, decreasing the population of circulating Th17 lymphocytes and increasing the population of regulatory T lymphocytes.

Ellipticine inhibits the proliferation of fibroblast-like synoviocytes in a dose-dependent manner. It also induces cell apoptosis through increased expression of pro-apoptotic genes (caspase-3) and decreased expression of anti-apoptotic genes (*Mcl*-1, *cyclin* D1, and *Bcl*-2) [49]. The effects of alkaloids in RA are summarized in Fig. 2.

Saponins

Saponins are compounds with steroidal or triterpene structures. They possess therapeutic activities related to the diuretic, digestive, antiplasmolytic activity [50]. These are non-protein nitrogen compounds that dissolve in water or foaming solution, thus having the property of emulsifying oils and producing hemolysis [51]. Table 2 lists studies with saponins in RA treatment.

Araloside A, a saponin extracted from the roots of *Aralia taibaiensis*, inhibited the proliferation of MH7A cells in vitro and decreased the production of IL-6, IL-8, and prostaglandin [10]. This study provided evidence that Araloside A can be a promising therapeutic agent in RA treatment.

Asperosaponin VI inhibits osteoclastogenesis by reducing the expression of genes and markers of signaling pathways that lead to osteoclast proliferation. It protected mice with collagen-induced RA from bone destruction and bone loss [15].

Tubeimoside I is a triterpenoid saponin isolated from *Bolbotemma paniculatum*. It demonstrated the ability to suppress the production of pro-inflammatory cytokines, such as IL-1β, IL-6, IL-8, and TNF-α, and decrease the expression of MMP-9 in vitro. In that same study, tubeimoside I was able to attenuate the harmful phenotypes of fibroblast-like synoviocytes in Wistar rats with

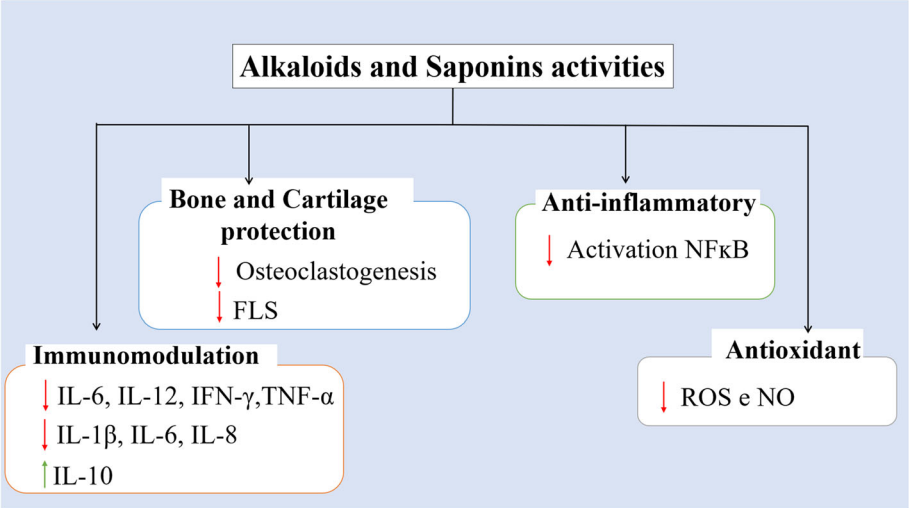


Fig. 2 Biological activities of alkaloids and saponins in RA. Legends: FLS- fibroblast-like synoviocytes, NFkB - nuclear factor κB, IL- interleukin, IFN - interferon, TNF - tumor necrosis factor, ROS - reactive oxygen species and NO - nitric oxide

collagen-induced RA, inhibiting cell proliferation and migration. This saponin showed anti-inflammatory activities and is a potential compound for the development of a drug against RA [16].

Pedunculoside is another compound that demonstrated favorable action in Wistar rats with collagen-induced RA. It inhibited the proliferation and migration of fibroblast-like synoviocytes and decreased the production of pro-inflammatory cytokines (IL- 1β, IL-6, IL-8, and TNF-α). The results suggest that the suppression of TNF-α stimulates the activation of p38 protein, which regulates cell kinase signaling, essential for apoptosis [52].

Madecassoside is a triterpenoid saponin present in *Centella asiatica*, which has anti-inflammatory activities. It inhibits the migration and invasion of fibroblast-like synoviocytes induced by IL-1β and activates NFkB signaling pathway in adjuvant-induced RA in Wistar rats [53].

Hecogenin is a saponin that demonstrated activities similar to madecassoside. It inhibits the migration of fibroblast-like synoviocytes and stimulating cell apoptosis by increasing the expression of caspases 3, 8, and 9 [66].

Platycodin D is a purified saponin from *Platycodi radix*. In mice with collagen-induced RAit decreased the production of IL-6 and TNF-α in a dose-dependent manner [54].

In an experimental model of collagen-induced RA in rats, the total saponins from *Rhizoma dioscoreae* Nipponicae increase the expression of the vascular endothelial growth factor, angiopoietin, and endothelial tyrosine kinase receptor. These results showed that the saponins inhibits angiogenesis in RA, leading to a better prognosis [55, 67]. Total saponins from *Psammosilene tunicoids* also demonstrated activity in combating RA inflammation through downregulation of IL-1β and TNF-α. Total saponins of *Anemone flacccida* Fr. Schmidt inhibit osteoclastogenesis resulting in decreased bone destruction due to collagen-induced RA in Wistar rats [56, 57]. The effects of alkaloids in RA are summarized in Fig. 2.

Conclusion and future directions

Conventional RA treatment produces mixed results: some cause undesirable side effects, while others can worsen the disease. Even a low-occurrin g side effect needs to be carefully considered against the drug's therapeutic potential. Conventional drugs that pass the initial tests and are approved for human use may not guarantee complete relief in RA cases.

Flavonoids, alkaloids and saponins from plants can delay or improve RA due to its antioxidant, anti-inflammatory, immunomodulatory, and enzymatic effects. These secondaries metabolites can provide abundant chemicals that minimize the disease. Thus, these secondaries metabolites can be promising alternative to the development of therapies capable of improving life quality in patients affected by RA.

In this review, we summarized chemical compounds isolated from plants that have therapeutic effects on RA models in vitro and in vivo. The mechanisms of action of these compounds in RA treatment mainly include anti-inflammatory, immunomodulatory, antioxidant, chondroprotective, and antiangiogenic activities. Most of the compounds possess good drug-like properties, valuable for further research. However, the pharmacological behavior of some compounds needs optimization.

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EMS and RCC make substantial contribution to conception and design. JCSS, RMO, RMR, MSSC and LGLN participated in the analysis and interpretation of data. LAMS, RNMN, ACSA, DCSCF, EFAS carried out acquisition of data and wrote the paper with input from all authors. All authors read and approved the final manuscript.

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