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REVIEW

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Mechanistic insights into anti-inflammatory and immunosuppressive effects of plant secondary metabolites and their therapeutic potential for rheumatoid arthritis

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Abstract

The anti-inflammatory and immunosuppressive activities of plant secondary metabolites are due to their diverse mechanisms of action against multifarious molecular targets such as modulation of the complex immune system associated with rheumatoid arthritis (RA). This review discussed and critically analyzed the potent anti-inflammatory and immunosuppressive effects of several phytochemicals and their underlying mechanisms in association with RA in experimental studies, including preliminary clinical studies of some of them. A wide range of phytochemicals including phenols, flavonoids, chalcones, xanthones, terpenoids, alkaloids, and glycosides have shown significant immunosuppressive and anti-inflammatory activities in experimental RA models and a few have undergone clinical trials for their efficacy and safety in reducing RA symptoms and improve patient outcomes. These phytochemicals have potential as safer alternatives to the existing drugs in the management of RA, which possess a wide range of serious side effects. Sufficient preclinical studies on safety and efficacy of these phytochemicals must be performed prior to proper clinical

studies. Further studies are needed to address the barriers that have so far limited their human use before the therapeutic potential of these plant-based chemicals as anti-arthritic agents in the treatment of RA is fully realized.

KEYWORDS
anti-arthritic drugs, anti-inflammatory, immune system, immunosuppressants, phytochemicals, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune illness that causes inflammation, stiffness, discomfort in the joints and characterized by swollen, red hands and feet. The disease can lead to severe pain, fluid buildup in the joints, shortness of breath, damage to internal organs (heart valves or lungs), diminished mobility and even death. The condition is characterized by synovial hyperplasia, an aggressive expansion of joint synovial tissue. This pathology degenerates articular joints, causing pain and edema (Merola et al., 2018). RA is associated with extensive degradation of cartilage and underlying bone that causes progressive disability, early death, and socioeconomic costs (Mueller et al., 2021). In addition to the systemic inflammation, patients with active RA also have higher mortality and morbidity rates than the general population due to a number of comorbidities, most notably cardiovascular diseases. The initiation and progression of RA are influenced by environmental and genetic factors (Fang et al., 2020). As a systemic disease, RA can still manifest even when joint damage is treated. Comorbidities, psychosocial deficiencies, and a reduction in well-being and quality of life that come along with RA's extra-articular symptoms must also be taken into account for a more thorough analysis of the burden of the disease (Raje et al., 2018).

There is no permanent cure for RA but early diagnosis and treatment with anti-inflammatory medications may help reduce symptoms over time. Different types of medications have been used to treat RA which include disease-modifying antirheumatic drugs (DMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, biologic response modifiers, and Janus kinase (JAK) inhibitors. These drugs act on the target of pathogenesis that cause joint degeneration and inflammation by different mechanisms. However, it is difficult to select the appropriate treatment due to variable efficacy between patients with RA (Merola et al., 2018). The current therapeutic approach is starting intensive therapy as soon as a diagnosis is made and escalating the medication in the goal of clinical remission while being guided by an evaluation of the disease activity. Some of the conventional and biologic disease modifying therapies are ineffective or only yield partial results. It is difficult to obtain sustained remission, which necessitates continued pharmacologic therapy. Patients with RA have a greater death rate than people in general. In addition, cardiovascular and other systemic complications remain to be serious problems. Thus, improvements in the discovery and development of new therapies with better outcomes should be facilitated by developments in the understanding of the etiology of the disease (Ikebuchi et al., 2018).

Research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs for RA. Natural products remain as safe and potential effective agents as alternative treatment for RA. Several plant-based compounds such as polyphenols, flavonoids, lignans, lactones, alkaloids, terpenoids, and glycosides have demonstrated strong immunosuppressive and anti-inflammatory properties (Hughes et al., 2017; Jantan et al., 2015). Several experimental studies have been conducted to evaluate the potency of natural-based compounds as anti-rheumatoid arthritis (anti-RA) agents. A number of reviews on the anti-inflammatory and immunosuppressive activities of medicinal plant extracts and plant-based compounds have been published recently (Jantan et al., 2015; Ghasemian et al., 2016; Hughes et al., 2017; Gandhi et al., 2021; Oliveira-Costa et al., 2022; Ali Reza et al., 2023; Habtemariam, 2023;). However, reviews on anti-inflammatory and immunosuppressive of plant secondary metabolites in relation to their potential use in the treatment of RA were scanty or even absent.

In this review, we gathered data on the anti-inflammatory and immunosuppressive effects of several phytochemicals and their underlying mechanisms in association with RA in in vitro and in vivo studies, including some preliminary clinical studies. This extensive review was conducted using scientific databases scanned from 2000 until now such as Google Scholar, Scopus, Science Direct, Elsevier, Springer, Pub Med, Taylor and Francis, and Wiley Online Library. The collected data underwent a rigorous analysis, and subsequent discussion focused on devising future strategies and adopting suitable viewpoints regarding the potential of plants as viable sources for developing new natural medicines to treat RA.

2 | THE PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

RA is an autoimmune disorder characterized by chronic inflammation of the joints, primarily affecting the synovial membranes. The pathogenesis of RA is not completely understood, but it is believed to involve a combination of environmental, genetic, and hormonal factors (Merola et al., 2018). The pathophysiology of RA involves immune dysregulation, synovial inflammation, synovial proliferation, pannus formation, joint destruction, and potential systemic effects. Understanding these processes helps in developing targeted treatment approaches for managing the disease. The etiology of this immunological dysregulation is hypothesized to be influenced by a confluence of

environmental and hereditary factors. RA involves a complex interplay of gene–environment that produces immune system dysregulation and breakdown self-tolerance. The most influential genetic variants in terms of predisposition to the development of RA have been attributed to the human leukocyte antigen (HLA) genes (Mueller et al., 2021). Genetic variation is responsible for between 50% and 60% of the chance of developing RA. Among them, the strongest genetic risk factor for RA is HLA-DRB1*01, *04, and *10 alleles (Derksen et al., 2017). The occurrence of a prevalent amino acid motif in these alleles is referred to as the shared epitope (SE). According to "shared epitope hypothesis", certain alleles of the HLA-DR4 RA and HLA-DR1 are involved in RA pathogenesis. In addition to the HLA region, SNPs PTPN22, PADI4, STAT4, TRAF1-C5, and TNFAIP3 have been implicated as causes of RA (Mueller et al., 2021). Environmental factors may also affect the progression and severity of RA. They act as a stimulating factor for antibody production in RA together with genes (Guo et al., 2018). There are several environmental factors associated with RA, such as air pollution, smoking, infections, and obesity (Barik & Bhatt, 2021; Gianfrancesco & Crowson, 2021).

Gene–environment interactions can lead to citrullination of cellular proteins. The genetically programmed amino acid arginine is converted to citrulline by peptidyl-arginine deiminase (PADs). Citrullination may arise under both physiological and pathological conditions (Derksen et al., 2017). Among the five PAD isoenzymes, PAD 2 and 4 are the most related to RA due to overexpressing in immune cells (Mondal & Thompson, 2019). Sometimes the immune cells fail to recognize these proteins as self-antigen thus they recognize citrulline containing regions of several proteins such as filaggrin, type-II collage, vimentin as foreign antigen. The peptide's binding affinity for the major histocompatibility complex (MHC) molecule was significantly enhanced when arginine was replaced with citrulline at the peptide-SE interaction site, as shown by experimental results. This modification increased the quantity of HLA peptide complexes on antigen presenting cells (APCs) (Derksen et al., 2017). These autoantigens are picked up by the APCs such as dendritic cells, macrophages, and activated B cells and get carried to the lymph nodes. Interaction of autoantigen with toll-like receptors (TLRs) on APCs initiate the immune response. Dendritic cells process antigens and then migrate to peripheral lymphoid tissue. Here, antigens are presented to T-cells, activating cellular immunity and antibody production in the adaptive immune system. Dendritic cells are important for maintaining immune control and tolerance. In RA, self-peptides are presented, leading to auto-reactive T-cells activation and the initiation of innate immune effector functions (Wehr et al., 2019).

In lymph nodes, CD4+ T-cells become activated by APCs through interactions between the T-cell receptor and class II MHC–peptide antigen with co-stimulation of CD28-CD80. Synovial CD4+ T-cells differentiate into several subsets of T helper with a distinctive profile. Increasing evidences demonstrate that RA development results due to an imbalance between CD4+ T-cell subsets with an excessive production of Th17 cells. Th17 cells are highly unstable and easily shift to Th1 cells (Kotake et al., 2017). Th17 cells play a necessary role in the development of RA by releasing several cytokines which include IL-17A, IL-17F, IL-22, IL-26, IFNγ, and the chemokine CCL20 (Fang et al., 2020; Giannini et al., 2020). Subsequently, IL-17A activates fibroblast-like synoviocytes (FLSs) and macrophage-like synoviocytes to enhance IL-26 release, which then stimulates the inflammatory cytokines IL-1β, IL-6, and TNF-α release by monocytes; these cytokines stimulate further differentiation of Th17 cells. Th17 cells is also able to stimulate osteoclast and synovial neovascularization which cause bone erosion (Fang et al., 2020). CD4+ T helper cells also activate B cells to differentiate into autoantibody-producing plasma cells. There is a nonstandard humoral immune response against citrullinated proteins in RA (Mueller et al., 2021).

There are high amounts of neutrophil extracellular traps (NETs) in the serum, synovial tissue, rheumatoid nodules, and skin in patients with anti-citrullinated protein antibodies (ACPA) (Fang et al., 2020). Neutrophils release NETs, which are designed to capture and eliminate pathogens. RA patients have higher levels of NETosis from both circulating and synovial fluid neutrophils than healthy controls. NETosis is also a source of citrullinated proteins which are targeted by ACPA (Giannini et al., 2020). Various synovial cells release cytokines which is central to the pathogenesis of RA. TNF-a and IL-6 play important roles in the RA pathogenesis without neglecting the impact of IL-1, VEGF, and IL-17 in the disease progression. TNF-α initiates cytokine and adhesion molecule development in endothelial cells, protecting synovial fibroblasts, promoting angiogenesis, suppressing regulatory T-cells, and inducing pain (Hess et al., 2011). Meanwhile, IL-6 facilitates activation of local leukocytes and production of autoantibody, and systemic effects which promote anemia, cognitive dysfunction, acute phase responses, and lipid-metabolism dysregulation. There is also abundantly expressed of IL-1 family cytokines (e.g., interleukin 1α, 1β, 18, and 33) in RA (McInnes & Schett, 2011).

All those pro-inflammatory cytokines are involved in synovial inflammation. Moreover, they promote angiogenesis, increasing the number of inflammatory cells in the joint and also stimulate pain receptor sensitizing pathways (Guo et al., 2018). The synovial intimal lining layer has fibroblast-like synoviocytes (FLS) that help maintain joint homeostasis through different mechanisms. FLS secrete important substances like hyaluronan, lubricin, and plasminogen activator. They also help control synovial fluid volume and regulate inflammatory responses. FLS also regulate leukocyte trafficking and maintain the joint capsule. RA is marked by the excessive growth of fibroblast-like synoviocytes (FLS). It is believed that the reduced ability of FLS to undergo apoptosis may contribute to their buildup in the joints (Fang et al., 2020). FLS population in synovium sublining layer experiences a substantial increase, resulting in the development of pannus. Pannus refers to synovial tissue proliferation, and it is thought to be a late, inactive, and irreversible symptom of RA (Cajas et al., 2019). The excessive growth of fibroblast-like synoviocytes (FLS) is attributed to the absence of contact inhibition. This absence leads to the release of inflammatory proteinases and cytokines, including tissue inhibitors of metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs). According to Guo et al. (2018), they create a milieu that facilitates the formation of neutrophils, and B cells and T-cells survival.

Inflammatory cytokines enhance the expression of RANK ligand (RANKL) on the surface of T-cell and activated fibroblast which allows

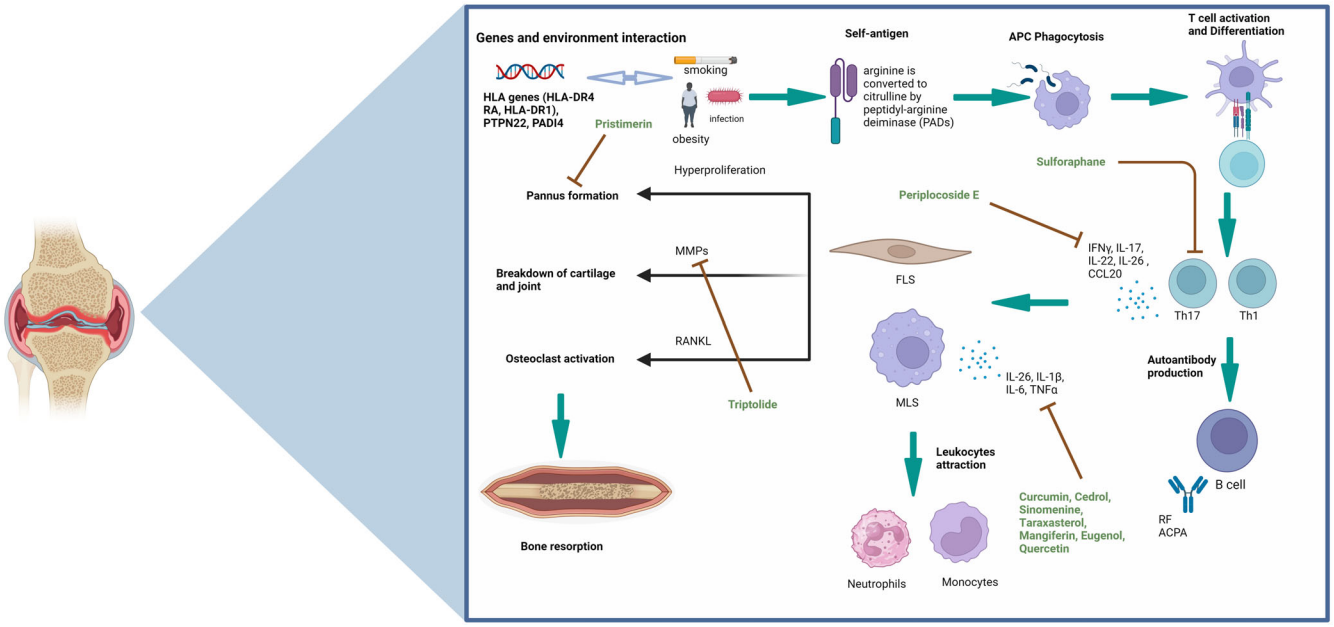

FIGURE 1 Pathogenesis of rheumatoid arthritis (RA) and mechanism of action of phytochemicals for treating RA. RA initiates by the interaction between genes and environment which induce citrullination of cellular proteins. Interaction of autoantigen with TLRs on APCs initiates the immune response. Th17 cells play a necessary role in the development RA by releasing several cytokines, including IL-17 which activates fibroblast-like synoviocytes (FLS) and macrophage-like synoviocytes (MLS). FLS produce matrix-degrading proteases (MMPs) which contribute to the breakdown of cartilage and joints which can be blocked by triptolide. Inflammatory cytokines enhance the expression of RANK ligand (RANKL) on the surface of T cell and activated fibroblast which allows them to bind RANK proteins on the surface of pre-osteoclasts, then convert them to activated osteoclast which is involved in bone destruction. Hyperproliferation of synovial tissue induces pannus formation which can be inhibited by pristimerin. In addition, B cells produce Rheumatoid Factor (RF) and anti-citrulinnated protein antibodies (ACPA) which contribute to the disease progression.

them to bind RANK proteins on the surface of pre-osteoclasts, then convert them to activated osteoclast which involve in bone destruction. It was suggested that ACPA binds to the osteoclast surface and enhances differentiation of osteoclast precursors and may directly affect osteoclasts. Moreover, bone erosion is developed by inhibiting Wnt pathway due to the action of elevated levels of DKK-1. Existing literature suggests that TNF-α is important in regulating the balance between bone degradation and bone generation. This occurs by increasing DKK-1 expression, which causes the internalization of Wnt receptors on osteoblast precursors (Derksen et al., 2017). Figure 1 illustrates the pathogenesis of RA.

3 | ANTI-ARTHRITIC DRUGS USED FOR RHEUMATOID ARTHRITIS

Anti-inflammatory and immunosuppressive agents have been employed as pharmacological interventions for the treatment of RA. The drug therapy for RA has evolved from analgesics to NSAIDs and corticosteroids, JAK inhibitors, and eventually to the synthetic and biological disease modifying antirheumatic drugs (DMARDs). These drugs used for RA act by different mechanisms to reduce inflammation in the joints, relieve pain, prevent or slow down joint damage, reduce disability, and other symptoms of RA. Early treatment for the disease with anti-arthritic drugs together with supportive treatments, and lifestyle changes can reduce the risk of joint damage. NSAIDs such as naproxen, ibuprofen, and celecoxib help to reduce inflammation, pain, and swelling in RA through inhibition of prostaglandins production by blocking the cyclooxygenases (COX). The strong anti-inflammatory corticosteroids are used for fast relief of pain in severe flare-ups and inflammation by suppressing the immune system. The JAK inhibitors target Janus kinases which are involved in the immune response and inflammation. Anti-inflammatory and immunosuppressive agents are often used as current therapeutic choices for RA; however, they can have considerable side effects (West, 2009). DMARDs (e.g. methotrexate, hydroxychloroquine, and sulfasalazine) help to slow down the progression of RA and prevent joint damage by primarily targeting the underlying autoimmune response in RA. Biologic response modifiers, such as adalimumab, rituximab, and etanercept, selectively target molecules implicated in the immune response, such as TNF-α and IL-6, with the aim of mitigating pain, inflammation, and joint deterioration in individuals with RA (Morinobu, 2020; Smolen et al., 2020).

Existing RA medications have limited effectiveness for some individuals and can cause significant adverse reactions with long-term use. Most RA medications have various side effects. DMARDs as immunosuppressants can inhibit the immune system and increase vulnerability to infections. Some DMARDs, such as methotrexate can

cause a variety of side effects from the most common gastrointestinal toxicity effects to less frequent liver damage and malignant diseases. Long-term use of NSAIDs may cause gastrointestinal problems and increase the risk of cardiovascular events such as strokes and heart attacks. The common side effects of corticosteroids include increased appetite, weight gain, weakening of the immune system, osteoporosis and muscle weakness. The side effects of biologics include allergic reactions, increased susceptibility to infections, and the development of antibodies against the medication. JAK inhibitors can suppress the immune system which may increase the risk of infections (Lin et al., 2020; Wang et al., 2018).

The introduction of biologic DMARDs in the late 1990s completely changed the treatment of RA. These consist of proteins and monoclonal antibodies that target immune pathway-related cell-surface molecules and inflammatory mediators like cytokines. TNF-α inhibitors have shown tremendous potential as treatment agents for RA, as they can reduce bone and cartilage loss and inflammation in the synovium. Unfortunately, long-term DMARD therapy for RA is linked to side effects, including increased risk of bacterial infections (*Listeria*, *Salmonella*, *Mycobacterium*, etc.) and viral infections (herpes zoster, hepatitis B reactivation from anti-TNF-α medication, etc.). Nasopharyngitis, urinary tract infections, and upper respiratory tract infections are among the side effects linked to tofacitinib. Furthermore, cardiac adverse events and cancers were side effects associated with baricitinib therapy. Elevated liver enzymes, hypertension, and even gastrointestinal perforation are linked to tocilizumab. Sometimes these side effects force the therapy to be stopped. Furthermore, there is still concern about the high cost of biological DMARDs. This influences disease outcomes in low-income countries by preventing access to the best care possible. The present synthetic and biological DMARDs have adverse effects, and their high cost makes it imperative to find novel RA treatment approaches. A possible approach is to combine low-dose DMARDs with phytochemicals to increase the effectiveness of RA therapy and reduce its adverse effects. Phytochemicals that have demonstrated beneficial synergistic benefits while lowering the adverse effects of the available RA treatments. A few combinations, including resveratrol, sinomenine, and coenzyme Q10, attracted a lot of attention due to their effectiveness in clinical trials when used as an adjuvant to MTX/standard DMARD therapy (Kour et al., 2021).

4 | ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE EFFECTS OF PHYTOCHEMICALS ON RHEUMATOID ARTHRITIS

Numerous studies have revealed a viable alternative in the form of plant-derived anti-inflammatory and immunosuppressive chemicals for potential use to treat RA (Sahoo & Banik, 2018). These phytochemicals have shown promise in inhibiting inflammation and improving RA symptoms, making them a potentially significant addition to the arsenal of therapies for this painful illness. This review covers the current status of research on plant-based anti-inflammatory and immunosuppressive phytochemicals and their possible involvement in the management of RA. Table 1 lists the phytochemicals with their anti-inflammatory and immunosuppressant effects and mechanisms of action, based on in silico, in vitro, and in vivo studies in cells and animal models of RA and preliminary clinical studies (Figure 2).

4.1 | Experimental studies

4.1.1 | Triptolide

Triptolide, found in *Tripterygium wilfordii* Hook F, is a diterpenoid epoxide with the potential to treat cartilage-related conditions such as RA. Liacini et al. (2005) determined the effect of triptolide on numerous cell types implicated in cartilage degradation. In primary bovine chondrocytes, triptolide at concentrations ranging from 100 to 600 nM could dose-dependently suppress the expression of MMP-13 and MMP-3 genes and downregulate MMP-13 protein expression. In human chondrosarcoma cell lines (SW1353) and human synovial fibroblasts, triptolide inhibited the induction of MMP-3 and MMP-13 RNA by pro-inflammatory cytokines, particularly TNF-α and IL-1β, with complete inhibition at higher concentrations and dose-dependent inhibition at lower concentrations. Moreover, triptolide has been reported to suppress IL-1β-promoted MMP-13 synthesis and secretion in both human and bovine cartilage explants, with inhibition detected at a dosage of 80 nM. These data imply that triptolide may have therapeutic potential for treating cartilage-related disorders such as RA by targeting MMP-3 and MMP-13 expression.

4.1.2 | Sinomenine

Yao et al. (2017) found evidence suggesting that sinomenine, an alkaloid of *Sinomenium acutum* (Thunb.) Rehder & E.H. Wilson stem might have therapeutic benefits for treating RA. In human RA fibroblast-like synoviocytes (RAFLS), sinomenine reduced the production of many inflammatory markers, including MyD88, TRL4, TNF-α, IL-6, and p-NF-κB p65. Moreover, sinomenine was able to inhibit the generation of NO and PGE_2, by inhibiting iNOS and COX-2 proteins expression. Sinomenine has been shown to suppress cell growth in human peripheral blood mononuclear cells (PBMCs) obtained from RA patients (Xu et al., 2021). Feng et al. (2019) reported that sinomenine lowered the arthritic index, inflammation, cartilage degradation, and bone erosion in mice with collagen-induced arthritis (CIA). Additionally, the levels of HIF-1α, VEGF, and ANG-1 dramatically decreased in the sinomenine-treated groups. Liu et al. (2018) demonstrated that at the doses of 50 and 100 mg/kg bw for 20 days, sinomenine significantly inhibited the progression of RA in CIA mouse model. The ability of sinomenine to strongly inhibit the pro-inflammatory cytokines production and gene expression related to joint and synovial inflammation suggested that it might have potential for development into an antirheumatic agent.

TABLE 1 Anti-inflammatory and immunosuppressant activities of phytochemicals in in vitro and in vivo models of rheumatoid arthritis and their preliminary clinical studies.

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
Triptolide	*Tripterygium wilfordii* Hook F	In vitro: primary bovine chondrocytes model, northern hybridization, and western immunoblot	Inhibited MMP-3 and MMP-13 gene expression generated by pro-inflammatory cytokines, and also downregulated MMP-13 protein expression dose-dependently	MMP-3 and MMP-13	Liacini et al. (2005)
		In vitro: chondrocyte model and northern hybridization	Inhibited the induction of MMP-3 and MMP-13 RNA by pro-inflammatory cytokines	TNF- α and IL-1β	
		In vitro: human synovial fibroblasts model and northern hybridization	Suppressed the induction of MMP-3 and MMP-13 RNA by pro-inflammatory cytokines	IL-1β.	
		In vitro: human and bovine cartilage explants study and western blotting	Inhibited MMP-13 protein secretion in both human and bovine cartilage explants	IL-1β promoted MMP-13	
Sinomenine	*Sinomenium acutum* (Thunb.)	RT-PCR and western blotting of Human rheumatoid arthritis fibroblast-like synoviocytes (RAFLS)	Inhibited IL-1β-induced production of NO and PGE_2 by inhibiting iNOS and COX-2 protein expression.	iNOS and COX-2	Yao et al. (2017)
			Prevented the expression of TNF-α, IL-6, TLR4, MyD88 and p-NF-κB p65 in IL-1β-stimulated RAFLS.	TNF-α, IL-6, TLR4, MyD88, and p-NF-κB p65	
		In vitro: PBMCs isolated from RA patients and cell viability assay	Inhibited the growth of RA patients' PBMCs by suppressed the secretion of inflammatory cytokines.	Th1, Th2, Th17	Xu et al. (2021)
		In vivo: CIA mouse model, histological and microscopy study of the knee joints of mice treated with sinomenine	Reduced inflammation, cartilage degradation, bone erosion, and arthritic index, and the number of CD31-positive cells in synovium.	CD31-positive cells	Feng et al. (2019)
		In vivo: CIA mouse model	Reduced levels of VEGF, HIF-1α, and ANG-1 in the synovium and in the peripheral serum	HIF-1α, VEGF, and ANG-1	
		In vivo: CIA animal model	Suppressed pro-inflammatory	Eotaxin-2, M-CSF, RANTES, and IL-1α,	Liu et al. (2018)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
			cytokine production and gene expression	IL-1β, TNF-α, KC, MCP-1 IL-6, GM-CSF, IL-12 p40.	
		Randomized controlled trial of RA patients	Reduced pro-inflammatory cytokines	TNF-α, IL-6, RANTES, MCP-1 GROα, Eotaxin-2, M-CSF, GM-CSF, IL-12p40, IL-1α, IL-1β	
			Increased anti-inflammatory cytokines	IL-10	
			Reduced CD14 + CD16+ monocytes	CD14 + CD16+ Monocytes	
Dictabretol A	*Dictamnus dasycarpus* Turcz	In vitro: mouse T and B lymphocytes.	Inhibited proliferation of lymphocytes by suppressing cell cycle transition from G1 to S phase	ERK1/2, NF-κB, and C-myc axis	Choi et al. (2016)
		In vivo: CIA mouse model and histological and microscopy study	Knee arthritis score and cartilage damage were considerably reduced and suppressed the blood levels of collagen-specific antibodies, TNF- α and IL-1β.	Collagen-specific antibodies, TNF- α and IL-1β.	
Cinnamaldehyde	*Cinnamomum cassia* Presland	In vitro: LPS-stimulated RAW 246.7 macrophages and ATP model, inflammatory factor assay, western blot, HIF-1α abatement and NLRP3 knock-down assay	Significantly decreased macrophage levels of IL-1β release at 12.5 μM of cinnamaldehyde by inhibiting NLRP3 and altering the HIF-1	NLRP3, HIF-1, and IL-1β	Liu et al. (2020)
		In vivo: SPF Sprague–Dawley (SD) Freund's adjuvant arthritis (AA) rats model, histological and microscopy study	Reduced paw oedema and abnormal joint section morphology in AA rats. The expression of NLRP3 and HIF-1 in the synovium of AA rats was considerably suppressed	NLRP3, HIF-1, IL-1β, and TNF-α.	
		In vitro: human PBMCs isolated from RA patients model, ELISA, DCF-DA cellular ROS assay and NO assay	Decrease levels of cytokines (TNF- α and IL-6), ROS and NO productions	ROS, NO, IL-6 and TNF-α.	Mateen et al. (2019)
Eugenol	*Cinnamomum verum*, and *Pimenta racemose*	In vitro: Human PBMCs isolated from RA patient model, ELISA, DCF-DA cellular ROS assay and NO assay	Decreased considerable amounts of cytokines (TNF-α and IL-6), ROS and NO production	TNF- α, IL-6, ROS, and NO	Mateen et al., 2019

(Continues)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
Pristimerin	Plants of Celastraceae	In vitro: synovial-infiltrating cells (SIC) harvested from Lewis male rats adjuvant arthritis (AA) model, flow cytometric analysis, and real-time quantitative PCR	Inhibited histopathological signs such as cartilage and bone damage in the joints and arthritic inflammation. by suppressing the pro-inflammatory cytokines and increase IL-10 and IFN- γ	IL-6, IL-17, IL-18, and IL-23, IL-10, and IFN-γ	Tong et al. (2014)
		In vivo: histological and microscopy study of the knee joints of mice treated with pristimerin	Prevented the advancement of arthritis and reduced arthritis severity in AA rats. The hind paws analysis revealed significant decrease in synovial membrane hyperplasia, synovial mononuclear cell infiltration, pannus development, and cartilage degradation.	Erythema and/or oedema, synovial membrane hyperplasia, synovial mononuclear cell infiltration, pannus formation, and cartilage degradation	Deng et al. (2015)
		Ex vivo assay: SD rat thoracic aortas	Dose-dependently decreased microvessel sprouting, suggesting that it prevented VEGF-induced angiogenesis	Microvessel sprouting	
		In vitro: human RAFLS model, chemotaxis assay, injury-healing migration assay	Reduced both cell survival and VEGF-induced RAFLS migration.	Cell viability	
Oxymatrine	*Sophora flavescens*	In vivo: histological and microscopy study of the knee joints of mice	Abrogated paw swelling, synovial hyperplasia, and arthritic scores. Increased weight loss and decreased the severity of CIA.	Volume of the hindpaw swelling (mm); arthritis score; synovial hyperplasia; and body weight	Ma et al. (2017)
		In vivo: CIA mouse model and ELISA	Significantly reduced the production of TNF-α and IL-17A	TNF-α and IL-17A	
		In vitro: Spleen lymphocytes from spleen that was removed from CIA rats that had been treated with oxymatrine	Upregulated mRNA level of FOXP3 and downregulated mRNA level of RORγt in rats with CIA.	FOXP3 and RORγt	
7′-(3′,4′-dihydroxyphenyl)-N-[(4 methoxyphenyl)	*Fissistigma oldhamii*	In vitro: purified primary T-cells induced by anti-CD3/28 mAb	Inhibited anti-inflammatory cytokine production	IFN-γ and IL-2	Hu et al. (2007)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
ethyl]propenamide (Z23)		In vitro: Use the Con A-induced splenocyte proliferation assay	Inhibited splenocytes proliferation induced by Con A	Splenocyte proliferation; T-cells	
		In vivo; murine $CD4^+$ T-cell DTH reaction model	Inhibited T-cell-mediated immune responses, effects on ear swelling in a DNFB-induced DTH reaction.	IFN-γ and IL-2	
		In vivo: type-II bovine collagen (CII)-induced arthritis (CIA) in DBA/1 mice	Reduced splenocyte proliferative activity and cytokine	IFN-γ and IL-2	
Stemucronatoside K (SMK)	*Stephanotis mucronata* (Blanco) Merr	In vitro: mitogen stimulated splenocytes from female ICR mice were immunized subcutaneously with OVA	Reduced LPS- and Con A- stimulated splenocyte proliferation	OVA-specific IgG, IgG_1, and IgG_{2b} antibody	Ye et al. (2008)
		In vivo: cytokine secretion from splenocytes in OVA-immunized mice	Inhibited OVA-, Con A-, and LPS-induced splenocyte proliferation in OVA-immunized mice.	IL-2, IFN-γ, and IL-4	
Periplocoside E (PSE)	*Periploca sepium* Bge	In vitro: spleens or draining lymph nodes primary T-cells stimulated by CD3 cross-linking. ELISA	Inhibited dose-dependently splenocytes proliferation induced by Con A	Proliferation of splenocytes	Zhu et al. (2006)
		In vitro: purified primary T-cells Con A-Induced Proliferation Assay	Suppressed proliferation of anti-CD3-induced primary T-cell, activated IL-2 Rα (CD25) expression, and production of cytokine at the transcriptional level	IL-2 Rα (CD25), IFN-γ, IL-2	
		In vivo: purified primary T-cells OVA-immunized mice with drug treatment	Inhibited OVA-induced proliferation and cytokine production from splenocytes	IL-2 and IFN-γ	
Isogarcinol	*Garcinia mangostana* L	In vivo; CIA animal model and ELISA	Reduced IL-6, IL-1β, IL-17 and TNF-α levels and the mean arthritis scores	IL-1β, TNF-α, IL-6, and IL-17	Fu et al. (2014)
		In vivo: severity of paws	Histopathological change in the joints, based on bone destruction scales or the synovitis and cartilage	Evidence of joint space narrowing, bone and cartilage erosion and synovial hyperplasia	
		In vivo: ear oedema model	Suppressed ear oedema induced by xylene	NO, iNOS, and COX-2 mRNA expression	

(Continues)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
Celasterol	*Celastrus aculeatus* Merrill	In vivo: male Lewis rats with hind paws histological examination.	Suppression of pannus formation, cartilage and bone destruction synovial mononuclear cell and infiltration in the joints of celastrol-treated rats	Mean arthritic score	Venkatesha et al. (2011)
		In vitro: Male Lewis rats with RT-PCR	Attenuation of IL-6, IL-17, and IFN-γ.	IL-6, IL-17, and IFN-γ	
Rhoifolin	*Rhus succedanea*	In vivo: Wistar rat model of CFA-induced arthritis with histopathological analysis	Overall health parameters such as weight loss and paw oedema showed significant improvement.	MDA, SOD, GSH and glutathione peroxidase	Peng et al. (2020)
		In vivo: CFA-induced arthritis in rat model with ELISA and qRT-PCR analysis Western blot analysis	Alleviated inflammation in CFA-induced arthritis and reduced IL-6, TNF-α, and IL-1β levels Significant reduction in the level of NF-κB compared to nontreated group	IL-1β, IL-6, TNF-α, NF-κB p65 and p-IκB	
Scopoletin	*Aster tataricus*, *Foeniculum vulgare*. and *Erycibe obtusifolia*	In vivo: fibroblast-like synoviocytes (FLS) from adjuvant arthritis rats	Suppressed proliferation of FLS production of IL-6 at both protein and mRNA levels Inhibited p38 MAPK, ERK, PKC and CREB phosphorylation	IL-6, ERK, PKC, P38 MAPK, and CREB	Dou et al. (2013)
Sulforaphane (SFN)	Brassicaceae family	In vitro: Cytokine assay on human T-cells of RA patients or healthy donors.	Inhibited TH17-related genes expression.	B-cell activating transcription factor, IL-22, IL17A, and IL17F.	Liang et al. (2018)
		Ex vivo: CFSE staining on RA T-cell proliferation	Inhibited TH17-related cells expression	IL-17A, IL-17F, and IL-22	
		Ex vivo: whole blood lymphocytes of RA patients with intracellular ROS levels analysis	Significant elevation of the level of intracellular ROS.	ROS level that determined by fluorescence intensity	
Tetrandrine	Chinese herb Han-Fang Chi	In vitro: Immunoprecipitation kinase assay and transfection assays on human peripheral blood T-cells	Downregulated IKK-IkBα-NF-κB signaling pathway and suppressed CD28-costimulated T-cells.	IkBα, IKKα, IKKβ kinase	Ho et al. (2004)
Rosmarinic acid	*Punica granatum*	In vivo: Wistar albino rats with Freund's complete adjuvant (FCA) treatment	Reduced paw volume, arthritic score, joint diameter, erythrocyte sedimentation rate, white blood cell count and increased hemoglobin, red blood cells and body weight.	Paw volume, RBCs and Hb, GSH, SOD, MDA and TNF-α	Gautam et al. (2019)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
Curcumin	*Curcuma* species	In vivo: CIA rat model	Suppressed inflammatory response in the joints of CIA mice and induced macrophage apoptosis	TNF-α, IL-17, IL-1β and TGF-β	Wang et al. (2019)
		In vitro: mice model	Inhibited lipoxygenase, NO, COX-2, iNOS, and NF-κB in TNF-α or IFN-γ stimulated macrophages and NK cells	Lipoxygenase, NO, COX-2, iNOS, NF-κB	Surh et al. (2001)
		In vitro: LPS-stimulated microglial cells	Suppressed NO production, TNF-α, IL-1β, IL-6 expression and release, and phosphorylation of PI3K/Akt, activation of NF-κB and expression of iNOS	NO, IL-6, iNOS, IL-1β, NF-κB, PI3K/Akt, and TNF-α.	Cianciulli et al. (2016)
		In vitro: LTA-activated microglial cells	Reduced production of TNF-α, NO, PGE_2, and COX-2 and iNOS expression	NO, PGE2, TNF-α, iNOS, and COX-2	Yu et al. (2018)
		In vivo: LPS-induced lactating mice	Reduced TNF-α, IL-6, IL-1β, TLR4 expression, IκB-α and NF-κB p65 phosphorylation and MPO activity	IL-6, TNF-α, IL-1β, TLR4, IκB-α and NF-κB p65.	Fu et al. (2014)
		In vivo: *Macrobrachium rosenbergii* that challenged with *Vibro alginolyticus*	Enhanced immune response.	Antimicrobial peptides (AMPs)	Alambra et al. (2012)
Quercetin	Numerous edible plants	In vivo: Female C57BL/6 mice	Decreased pro-inflammatory secretions in RA rats by inhibiting neutrophil activity.	IL-4, IL-6, INF-γ, a TNF-α, and NETs.	Yuan et al. (2020)
		In vivo: CFA rat model	Inhibited paw volume significantly and suppressed joint inflammation in CFA rats model	TNF-α	Gokhale et al. (2019)
Rutin	Grapes, oranges, cherries, and apricot	In vivo: CFA rat model induced by bovine type-II collagen	Reduced the severity of arthritis by downregulating the expression of oxidative stress markers	NO, Peroxide (PO), NF-κB and iNOS	Gul et al. (2018)
Resveratrol	Fruits and vegetables	In vivo: rats induced by Bovine type-II collagen (BIIC)	Reduced the level production of pro-inflammatory cytokines and ROS	IL-1β, IL-6, MCP-1, and TNF-α	Yang et al. (2018)
		Clinical study: using systolic heart failure patients with	Reduced pro-inflammatory cytokines	IL-1 and IL-6	Gal et al. (2021)

(Continues)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
		placebo-controlled study, randomized, single-center, double-blind			
		In vivo: CIA mouse model	Suppressed the progression of RA and suppressed the pro-inflammatory production	Eotaxin-2 secretion, GM-CSF, KC, IL-12, IL-6, p40, IL-1α, TNF-α, and IL-1β	Liu et al., 2018
Salicin	*Alangium chinense*	In vivo: CIA rat model	Reduced the infiltration of inflammatory mediator and oxidative stress in the ankle joinT-cells	The level of clinical score arthritis	Zhai et al. (2018)
α-Mangostin	*Garcinia mangostana*	In vivo: adjuvant-induced arthritis (AA) in rat	Reduced the release of pro-inflammatory cytokines and by decreasing the endogenous pathogenic factor and controlling immune homeostasis	TNF-α and IL-1β	Zuo et al. (2018)
Rosmanol and Carnosol	*Callicarpa longissima* (Hemsl.) Merr	In vivo: CIA DBA/1 mice model	Synergistic effect in ameliorating RA by suppressing pro-inflammatory cytokines.	IL-6, monocyte chemotactic protein 1 (MCP-1), and TNF-α	Li et al. (2022)
Mangiferin and Glycyrrhizic acid	*Mangifera indica* L	In vivo: adjuvant-induced arthritis (AIA) rat model	Recovered energy metabolic disorders and alleviated disease severity in AIA-M rats	PKA-ADCY5-PPARγ-PGC 1α-UCP1-PRDM16 signal axis	Mao et al. (2022)
		In vitro: LPS-stimulated THP-1 human macrophages	Suppressed TNF-α expression.	TNF-α	Brito et al. (2019)
		In vitro: in silico docking simulation using colon tissue in DSS induced colitis in BALB/c mice	Strong binding affinity against TNF-α by forming a stable complex to TNF-α with binding energy ranging from −8 to −7.6 kcal/mol	TNF-α	Somani et al. (2016)
Taraxasterol	*Taraxacum* officinale	In vivo: CIA mice model	Inhibited pro-inflammatory cytokines production by modulation of NF-κB and NLRP3 inflammasome pathways activation	IL-6 and TNF-α	Chen et al. (2019)
Stigmasterol	Widely distributed in plants	In vivo: Rats induced by collagen type-II (CII)	Ameliorated inflammation and arthritic index, suppressed pro-inflammatory cytokine production	NF-kB mRNA level, p-IKBα, iNOS and COX-2	Ahmad Khan et al. (2020)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
Ursolic acid	Widely distributed in plants	In vivo: CFA rat model	Suppressed RA by suppressing production of pro-inflammatory cytokine and COX 1 and 2 activities	IL-1β and TNF-α.	Ahmad et al. (2018)
Cedrol	Genera *Cupressus* (cypress) and *Juniperus* (juniper).	In vivo: CFA rat model	Suppressed the release of cytokines and the production of oxidative stress in joint	TNF-α, IL-1β, and MDA.	Forouzanfar et al. (2022)
Theaflavin-3,3′-digallate	Black tea	In vivo: Freund's Adjuvant in DBA/1 mice	Reduced pro-inflammatory cytokine production.	TNF-α, IL-1β, and IL-6.	Zhang et al. (2023)
Zerumbone	*Zingiber zerumbet*	In vivo: CFA rat model	Reduced swelling of the foot and arthritic index in CFA rat model, decreased the profile of oxidative stress in tissue and suppressed the pro-inflammatory cytokine production.	Lipid peroxidase, superoxide dismutase, hydrogen peroxide, TNF-α, IL-1β, and IL-6	Alsaffar et al. (2023)
		In vitro: LPS-stimulated human macrophages	Inhibited pro-inflammatory mediator production	COX-2, PGE_2, TNF-α and IL-1β	Haque et al. (2018)
Pipernigramide and Piperine	*Piper nigrum* L.	In vitro: ELISA and RT-PCR also in silico docking simulation using IL1β-stimulated fibroblast-like synoviocytes derived from RA patients	Piperine showed the highest binding affinity (−8.88 kcal/mol) with the COX-2 protein thus inhibited COX-2 protein expression.	COX-2 expression	Bang et al. (2009), Chy et al. (2020)
		In vitro: LPS-activated RAW 264.7 cells	Inhibited production of NO.	NO	Xu et al. (2023)
Naringenin	Tomatoes and citrus fruits	Randomized controlled trial: Children with bronchial Pneumonia	Reduced pro-inflammatory cytokines	IL-6, IL-8, and TNF-α	Yao et al. (2021)
		Randomized controlled trial: Children with bronchial Pneumonia	Increased production of anti-inflammatory cytokines	IL-10	
Xanthohumol	*Humulus lupulus*	Placebo-controlled single-blinded cross-over study of lipoteichoic acid-induced PBMCs from healthy individuals	Suppressed production of pro-inflammatory cytokines.	IL-6, IL-1β, and sCD14 protein release	Jung et al. (2022)
Cannabidiol	*Cannabis sativum* L.	Pilot randomized, parallel arm, double-blind study using LPS-stimulated PBMCs from healthy individuals	Reduced pro-inflammatory cytokine production	TNF-α	Hobbs et al. (2020)
Licochalcone A	*Glycyrrhiza inflata*	In vivo: RASFs isolated from the synovium of	Inhibited the proliferation and arrested the cell cycle	mRNA, IL-1β, and IL-6	Su et al. (2018)

(Continues)

TABLE 1 (Continued)

Compounds	Sources	Study design/method with subjects	Immunosuppressant activities	Parameter/ mediator affected	References
		CIA model of DBA mice	Increased antioxidant enzyme expression including NQo1 and HO-1 through Keap1-Nrf2 signaling activation, and reduced ROS production	ROS, HO-1 and NQO1	
Carvacrol	*Thymus vulgaris*, *Origanum vulgare*, *Citrus aurantium bergamia*, *Lepidium flavum*	In vitro: RASFs	Inhibition on LPS-induced cell proliferation and migration of RA-FLSs.	TNF-α, IL-6, and L-8	Li et al. (2019)
		In vivo: adjuvant-induced arthritis (AIA) rats	Anti-inflammatory effect by reduced erythrocyte sedimentation rate, NO production, clinical severity score, and IL-17 gene expression	Clinical severity score, erythrocyte sedimentation rate, NO, IL-17	Gholijani et al. (2020)
		In vivo: mouse tolerogenic dendritic cells	Stimulated the activity of regulatory T-cells	T-cell responses	Spiering et al. (2012)
Perillyl alcohol	Citronella, lavender, peppermint, spearmint, and celery seeds	In vitro: RAW 264.7 cells stimulated with LPS	Inhibited ROS, NF-κB, and Nrf2 signaling, reduced nitrate, pro-inflammatory cytokines, PGE_2, and COX-2 levels	TNF-α, IL-6, IL-1β, COX_2, PGE_2, ROS, nitrate, and Nrf2 and NF-κB signaling	Puppala et al. (2022)
		In vivo: CFA-induced inflammation rat model	Reduced CFA-induced inflammation by restoring arthritic index, body weight, nitrosative, and lipid peroxidation	COX-2, iNOS and NF-κB, SOD2, and Nrf2	
β-D-Mannuronic acid	Brown marine phytoplankton or seaweed	Clinical trial: RA patients	Reduced miR-155 expression.	miR-155	Mortazavi-Jahromi et al. (2020)
		Clinical trial: RA patients	Increased the expression levels of SOCS1 and SHIP1 genes	SOCS1 and SHIP1 genes	

4.1.3 | Dictabretol A

In an in vitro model utilizing mouse T and B lymphocytes, dictabretol A, a glabretal-type triterpenoid isolated from *Dictamnus dasycarpus* Turcz, root bark, was found to selectively suppress lymphocyte growth by preventing the transition of cell cycle from G1 to the S phase. This was achieved by inhibiting the ERK1/2, NF-κB, and C-myc axis, and the effective concentration was determined to be 2 μM. In a CIA mouse model, the knee joints of eight-week-old DBA1/J mice treated with dictabretol A, revealed considerable decrease in the knee arthritis score and cartilage damage compared with the control group. Moreover, blood levels of inflammatory cytokines, such as IL-1β and TNF-α, as well as collagen-specific antibodies (IgG1 and Ig2a), were much lower in the dictabretol A-treated group than in the control group, as confirmed by ELISA (Choi et al., 2016). The effectiveness of dictabretol A in decreasing the knee arthritis score and cartilage damage in mice suggested that the compound could potentially be developed into a medicinal agent for the treatment of RA.

4.1.4 | Cinnamaldehyde

Cinnamaldehyde, a major compound in *Cinnamomum cassia* Presland, has shown potential anti-inflammatory activity in numerous experimental models. In an in vitro model employing RAW 246.7

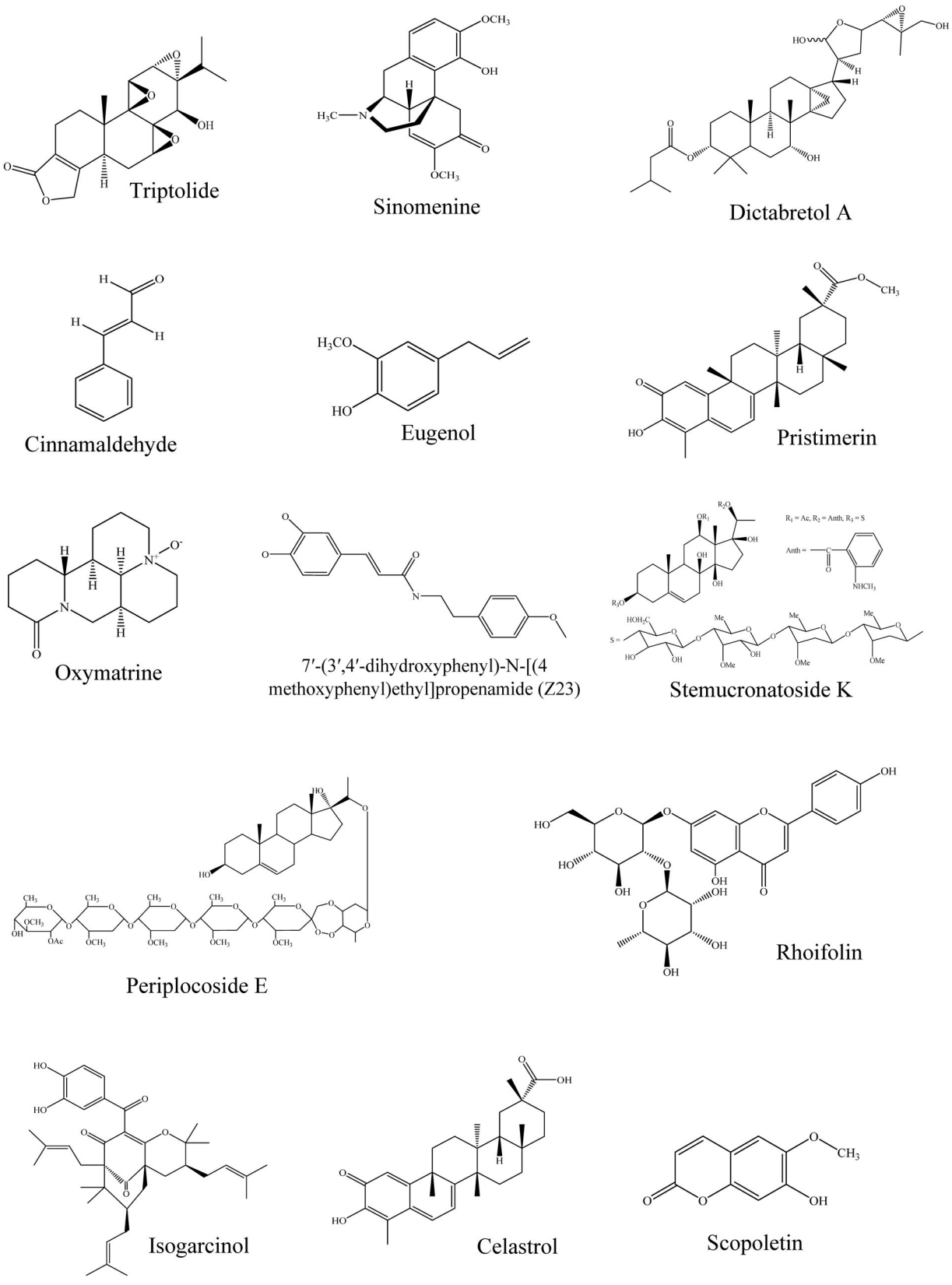

FIGURE 2 Chemical structures of anti-inflammatory and immunosuppressant phytochemicals with therapeutic potential on rheumatoid arthritis.

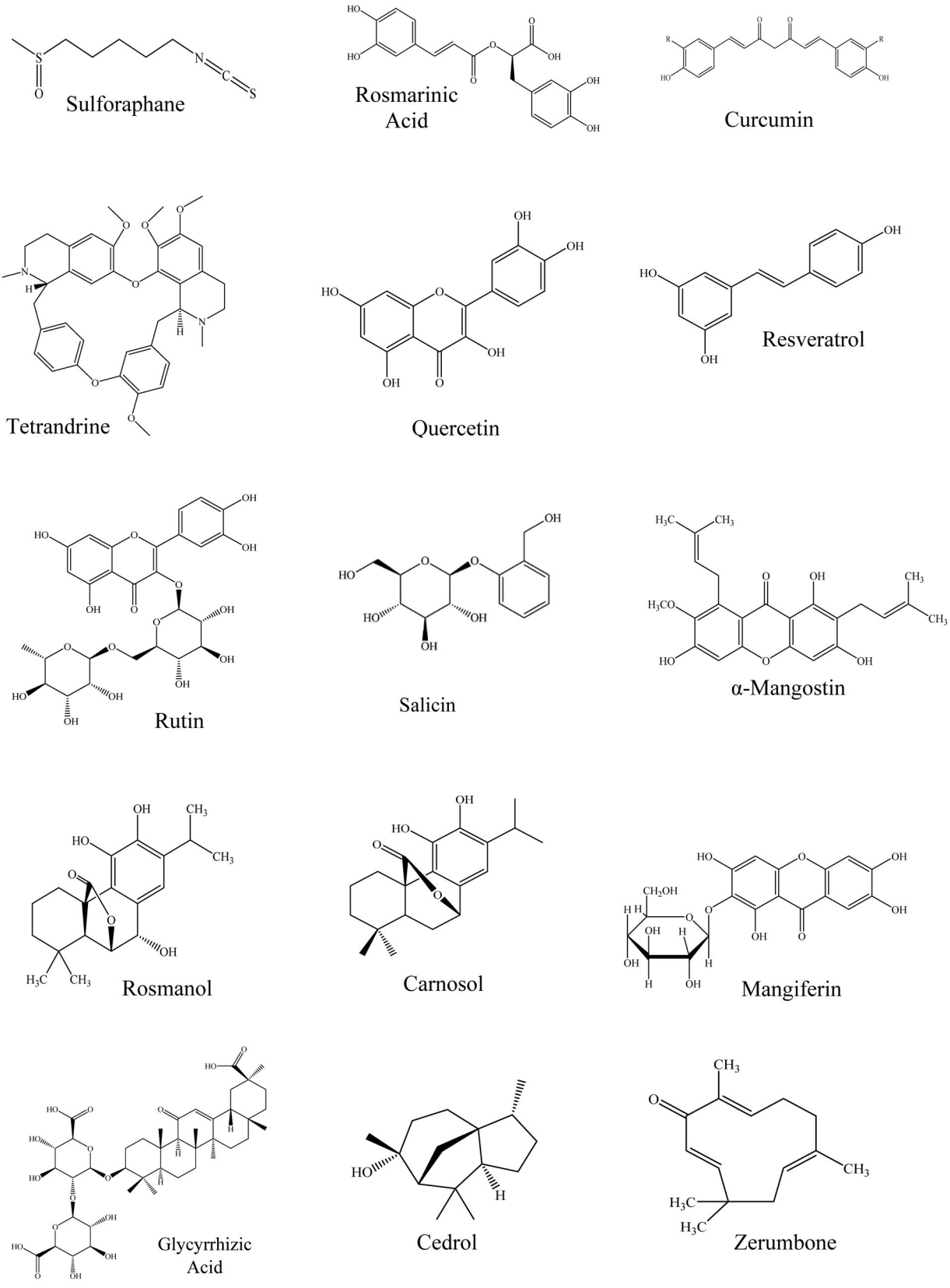

FIGURE 2 (Continued)

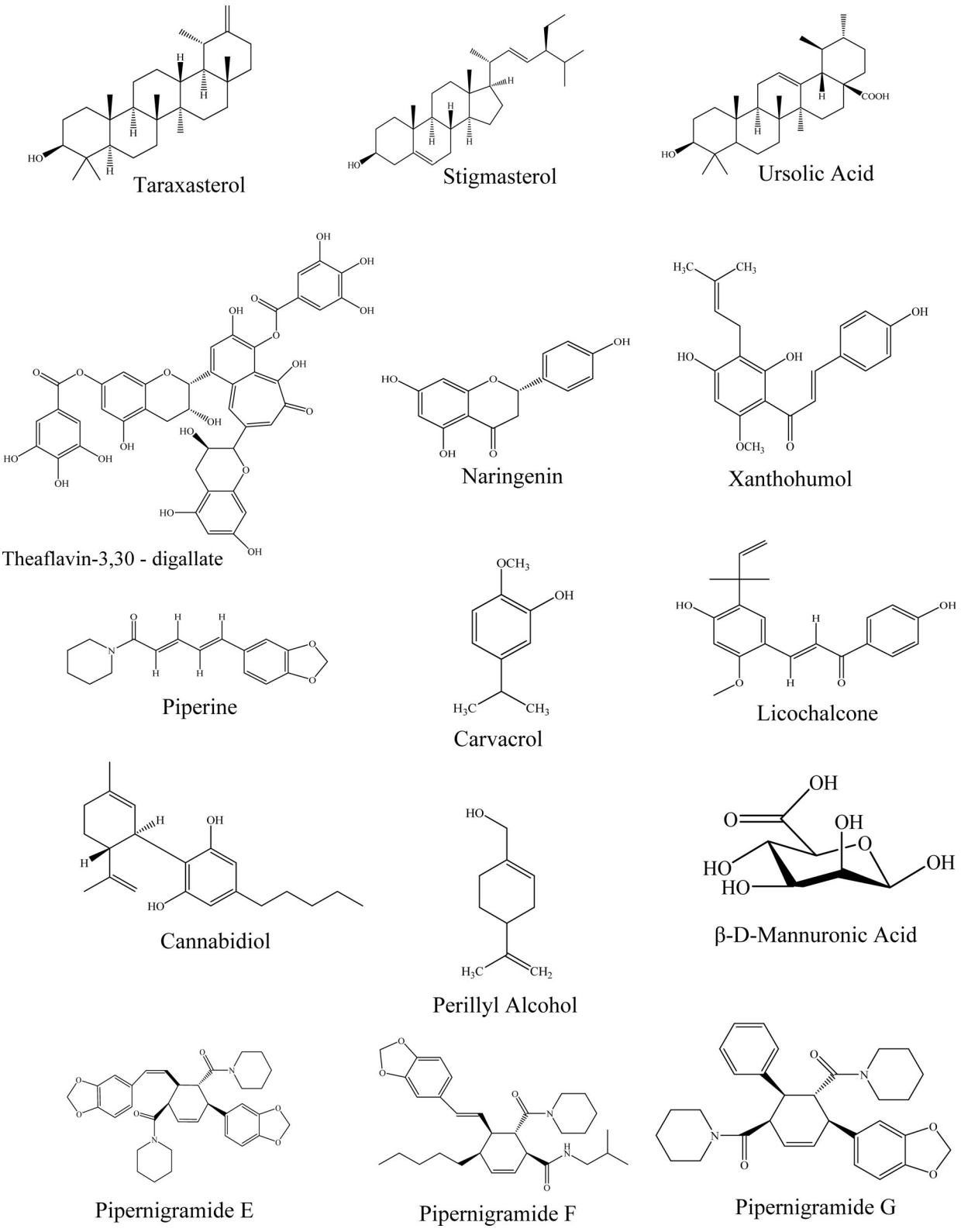

FIGURE 2 (Continued)

macrophages challenged with LPS and ATP, cinnamaldehyde dramatically lowered the amounts of IL-1β produced by macrophages and greatly inhibited the production of nucleotide-binding domain, pyrin domain–containing-3 (NLRP3), leucine-rich–containing family, and hypoxia-inducible factor-1 (HIF-1) in the synovium. Similarly, in an in vivo model using SPF Sprague–Dawley (SD) rats with Freund's adjuvant arthritis (FAA), cinnamaldehyde reduced paw oedema and abnormal joint section morphology, as well as significantly suppressed levels of IL-1β in the peripheral blood and expression of NLRP3 and HIF-1 in the synovium (Liu et al., 2020). NLRP3 and HIF-1 play important role in inflammation in RA. NLRP3 is a protein complex that triggers the production of IL-1β (Yin et al., 2022), whereas HIF-1 is a transcription factor that affects the expression of genes involved in inflammation and tissue damage (Li et al., 2016). In RA, the levels of NLRP3 and HIF-1 are elevated, resulting in the overproduction of IL-1 and other pro-inflammatory chemicals. Hence, blocking NLRP3 and changing the HIF-1 axis may be a possible method to decrease inflammation and cure RA. In contrast, Mateen et al. (2019) demonstrated that cinnamaldehyde dose-dependently lowered cytokines, NO and ROS production in PBMCs obtained from RA patients. The effectiveness of cinnamaldehyde to suppress the production of IL-1β, NLRP3, and HIF-1 in in vitro and in vivo in the synovium in RA models suggested that it has potential as an anti-arthritic agent for treatment of RA.

4.1.5 | Eugenol

Eugenol is a naturally occurring phenylpropanoid that can be found in a number of species, including cloves (*Syzygium aromaticum*), cinnamon (*Cinnamomum verum*), and bay rum leaves (*Pimenta racemose*). The anti-inflammatory activity of eugenol was evaluated in human PBMCs isolated from RA patients using an in vitro model (Mateen et al., 2019). Findings from ELISA, DCF-DA cellular ROS, and NO assays indicated that eugenol at doses of 10, 20, and 40 μM significantly and dose-dependently reduced the production of TNF-α, IL-6, NO, and ROS. The significant anti-inflammatory activity of eugenol indicated that it has potential for further development into an anti-arthritic agent to treat RA.

4.1.6 | Pristimerin

Pristimerin, a triterpenoid found in the plants of Celastraceae family, has also demonstrated some anti-arthritic properties. Tong et al. (2014) demonstrated that pristimerin successfully inhibited histological evidence of arthritic inflammation and cartilage and bone destruction in joints in an in vivo model of autoimmune arthritis (AA) mice. At the onset of AA, mice that received intraperitoneal injections of 1 mg/kg pristimerin daily for 5 days exhibited these outcomes. Moreover, in an in vitro model, synovial-infiltrating cells (SIC) extracted from AA rats and treated with pristimerin displayed reduced levels of pro-inflammatory cytokines and transcription factors and elevated levels of IL-10 and IFN-γ, which suppressed IL-17. Moreover, Deng et al. (2015) also explored the effects of pristimerin in arthritis but in a different set of experiment method. They demonstrated that pristimerin has been found to have therapeutic potential for arthritis and angiogenesis. In an in vivo model using SD rats with induced arthritis, daily intraperitoneal injections of 0.4 and 0.8 mg/kg of pristimerin from day 11 to 24 after the initial immunization prevented the advancement and reduced the severity of arthritis, as evidenced by erythema and/or oedema. The hind paw examination showed reduced mononuclear cell infiltration in the synovial tissue, synovial membrane hyperplasia, pannus formation, and cartilage degradation. Pristimerin also revealed a dose-dependent reduction in micro vessel sprouting in an ex vivo study of rat aortic rings cultivated in the presence of VEGF. Additionally, in an in vitro investigation using human RAFLS indicated that pristimerin decreased cell survival and VEGF-induced migration in a dose- and time-dependent manner. The ability of pristimerin to successfully inhibit arthritic inflammation, pannus formation, cartilage, and bone destruction in joints in different animal models for arthritis indicated that the compound has potential to be developed into an anti-RA agent.

4.1.7 | Oxymatrine

Oxymatrine, a monosomic alkaloid isolated from *Sophora flavescens* Ait, has shown potential in the treatment of RA. In a study conducted by Ma et al. (2017) on 5–6-week-old SD male rats, oxymatrine significantly reduced the severity of CIA, as evidenced by a marked decrease in synovial hyperplasia, arthritic scores, paw swelling, and body weight loss. Moreover, as demonstrated by ELISA in the same CIA mouse model, oxymatrine decreased IL-17A and TNF-α production significantly. In addition, real-time quantitative PCR and western blot analysis of isolated spleen cells from CIA-treated rodents with oxymatrine revealed elevated mRNA level of FOXP3 and decreased RORγt mRNA level. All of these discoveries were made in rodents injected with bovine type-II collagen mixed with adjuvant and treated intraperitoneally once daily for 43 days with 100 and/or 50 mg/kg oxymatrine. FOXP3 and RORt are two proteins that aid in regulating the equilibrium between Tregs and Th17 cells. In RA, the equilibrium is thrown off, with fewer Tregs and more Th17 cells contributing to inflammation and joint degeneration. This is partly due to reduced FOXP3 expression in Tregs and increased RORγt expression in Th17 cells (Furuyama et al., 2022; Jiang et al., 2021; Kondo et al., 2015). Hence, the upregulation of FOXP3 and downregulation of RORγ may be a viable therapeutic strategy for RA. As it also significantly reduced the CIA in rodents and suppressed IL-17A and TNF-α production, oxymatrine might be a good choice for development into an anti-RA agent.

4.1.8 | 7′-(3′,4′-dihydroxyphenyl)-N-[(4-methoxyphenyl)ethyl]propenamide

Traditional Chinese Medicine (TCM) has approved *Fissistigma oldhamii* for the treatment of RA in China. Several compounds from the plant

exhibited potent immunosuppressive effects in previous studies, but most were challenging to isolate in sufficient quantities for further research. 7′-(3′,4′-dihydroxyphenyl)-N-[(4-methoxyphenyl)ethyl]propenamide (Z23), a newly isolated amide from the plant, has been investigated for its in vivo and in vitro immunosuppressive effects on T-cells. Z23 suppressed proliferation of T-cell with low cytotoxicity. In vitro, Z23 inhibited production of IL-2 and IFN-γ (Th1 cytokines) dose-dependently by anti-CD3/28 mAb induced T-cells, indicating that Z23 could treat diseases associated with these cytokines. IL-12 promotes Th1 T-cell production, cytokine secretion, polarisation, and T-cell proliferation. These findings suggested that Z23 immunosuppressed T-cell activation rather than antigen presentation. In a murine delayed-type hypersensitivity (DTH) model, Z23 inhibited T-cell function. Z23 reduced 2,4-dinitrofluorobenzene (DNFB)-induced ear swelling in a dose-dependent manner. Anti-RA studies using 25 mg/kg intraperitoneal injection of Z23 demonstrated reduced incidence, severity, and development of CIA, a well-established murine model of human RA. CIA mice treated with Z23 showed significantly reduced splenocyte proliferative activity (Hu et al., 2007). The significant immunosuppressive effect of Z23 as shown in its ability to inhibit T-cell function and suppressed CIA in mice indicated that it has potential to be developed into a therapeutic agent to treat RA.

4.1.9 | Stemucronatoside K

Ye et al. (2008) examined the immunosuppressive activity of a novel C_{21} steroidal glycoside, stemucronatoside K (SMK), isolated from the roots of *Stephanotis mucronata* (Blanco) Merr., which has been used in TCM to treat RA. An in vitro proliferation assay indicated that intraperitoneal injection of SMK at various concentrations (2.5, 5, and 10 mg/kg) once daily for 10 days significantly suppressed LPS-. OVA- and Con A-induced splenocyte proliferation in ovalbumin (OVA)-immunized ICR mice. In comparison with the control group, SMK was found to substantially inhibit the levels of OVA-specific IgG, IgG2b, and IgG1 antibody titers. Additionally, OVA-induced IL-2, IFN-γ, and IL-4 production from splenocytes in OVA-immunized mice was significantly reduced by SMK, indicating that SMK was effective at reducing production of antigen-specific T-cell of Th1/Th2 cytokines in the mice. Although the findings have demonstrated that SMK exhibited significant immunosuppressive activity, further study is required to evaluate its potential as an antirheumatic agent to treat RA.

4.1.10 | Periplocoside E

Periplocoside E (PSE), a pregnane glycoside, was found to be the most potent immunosuppressive compound isolated from *Periploca sepium* Bge. Zhu et al. (2006) conducted in vitro and in vivo studies on the immunosuppressive effects of PSE. They demonstrated that PSE inhibited Con A-induced splenocyte proliferation and mixed-lymphocyte culture reactions significantly at innocuous concentrations (<5 μM). PSE prevented a delayed-type hypersensitive (DTH) reaction in mice. In vivo treatment with PSE inhibited the proliferative effects of OVA and splenocyte production of the cytokines IL2 and IFN-γ. Purified T-cells from OVA-immunized mice treated with PSE exhibited a low capacity for activation by OVA plus conventional APC stimulation in vitro. In response to anti-CD3 stimulation, PSE inhibited, in a dose-dependent manner, primary T-cell proliferation, IL-2R (CD25) activation, and cytokines production at the transcriptional level. PSE was extremely specific and substantially inhibited the activation of Jun N-terminal kinase and extracellular signal-regulated kinase in anti-CD3-stimulated T-cells but had no effect on the activation of p38. The potent immunosuppressive effect of PSE in attenuating T-cell activation in vitro and in vivo studies revealed its potential as an anti-arthritic agent to treat RA.

4.1.11 | Isogarcinol

Fu et al. (2014) investigated the immune-regulatory and anti-inflammatory activity of isogarcinol, a polyisoprenylated benzophenone from the fruit of *Garcinia mangostana* L. on CIA, in addition to its mechanism of action in the treatment of RA. Isogarcinol's mechanism of action involved the downregulation of inflammatory and autoimmune responses. Oral administration of isogarcinol to CIA mice significantly decreased clinical scores, halted bone and cartilage erosion, and decreased serum levels of inflammatory cytokines. By inhibiting NF-κB expression, isogarcinol prevented xylene-induced ear oedema in mice and decreased NO content, iNOS, and COX-2 mRNA expression in vitro. Isogarcinol additionally inhibited NFAT activity and IL-2 expression. The strong anti-inflammatory and immunosuppressive effects of isogarcinol in CIA mice suggested that it has potential to be developed into a medicinal agent for the treatment of RA.

4.1.12 | Celastrol

In a rat adjuvant-induced arthritis model of human RA, celastrol, a pentacyclic nortriterpene quinone isolated from *Celastrus aculeatus* Merrill, significantly reduced adjuvant-induced arthritis severity and suppressed IFN-γ, IL-17, and IL-6 responses (Venkatesha et al., 2011). In contrast to the control rats, celastrol-treated rats displayed significant decrease in synovial mononuclear cell infiltration, pannus development, and cartilage and bone deterioration within their joints. The expression of cytokines in the lymph node cells (LNC) was determined using quantitative RT-PCR. Celasterol at concentrations of 0.05 and 0.1 μM reduced Bhsp65-induced IL-17 and IFN-γ mRNA expression by 2.1 and 2.5-fold, respectively ($p < 0.05$). Cytokine expression was determined following stimulation of spleen adherenT-cells with sonicated *Mycobacterium tuberculosis*. In rats administered with celastrol, pSTAT3 expression was reduced relative to untreated controls, whereas LNC cultures lacking Bhsp65 exhibited an ex vivo expression profile. In arthritic joints of Lewis rats, fibroblast-like synoviocytes secreted mediators of inflammation and tissue damage. However, celastrol selectively suppressed these mediators and inhibited tissue

damage mediators. Antibodies against Bhsp65 and aCCP were lower in rodents treated with celastrol compared with rats fed only water. The ability of celastrol to significantly reduce adjuvant-induced arthritis severity in rats by decreasing the synovial mononuclear cell infiltration, pannus development, and cartilage and bone deterioration in joints might suggested its potential as a candidate for development as an anti-arthritic agent for treatment of RA.

4.1.13 | Rhoifolin

Rhoifolin, a flavonoid found in *Rhus succedanea*, is known for its anti-inflammatory and antioxidant activities. Peng et al. (2020) determined the effect of rhoifolin on a rat model of CFA-stimulated arthritis. Rhoifolin given at concentrations of 10 and 20 mg/kg significantly improved numerous health parameters, including the reduction of paw edema and weight loss prevention. The observed increase in morphological parameters is consistent with the histological study, which revealed significant morphological changes. There were changes in the intracellular concentrations of SOD, malondialdehyde (MDA), glutathione (GSH), and glutathione peroxidase within articular cartilage tissue. Notably, the administration of rhoifolin significantly decreased oxidative stress. The pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), gene expression, and intracellular protein concentration levels were also significantly downregulated. The levels of NF-κB p65 and p-IκB-a were significantly decreased, demonstrating significant attenuation of the NF-κB network. NF-κB might likely be involved in rhoifolin's antioxidant and anti-inflammatory properties. Further research is necessary to investigate the potential of rhoifolin as a candidate for development into an anti-arthritic agent to treat RA.

4.1.14 | Scopoletin

Scopoletin, a coumarin isolated from numerous plants including *Erycibe obtusifolia*, *Aster tataricus*, *and Foeniculum vulgare*, has demonstrated ability to reduce synovial inflammation and bone and cartilage degradation in rodents with adjuvant arthritis (AA). Dou et al. (2013) investigated the effect of scopoletin on IL-6 production from fibroblast-like synoviocytes (FLS). IL-1β (10 ng/mL) was used to stimulate FLS, which was isolated from AA rat synovial membrane tissues. Scopoletin at concentrations of 15, 30, and 60 μM, marginally inhibited FLS proliferation, whereas it substantially reduced IL-6 production at both the mRNA and protein levels. In addition, phosphorylation of p38 MAPK, ERK, PKC, and CREB was prevented. These results suggested that scopoletin probably inhibited IL-6 production from FLS via the MAPK/PKC/CREB pathways to exert its anti-RA effects.

4.1.15 | Sulforaphane

Sulforaphane, an isothiocyanate found in Brassicaceae plants such as broccoli, cauliflower, and kale induced a pro-oxidative state in non-transformed human T-cells from RA patients or healthy donors (Liang et al., 2018). This increase led to an elevation in level of intracellular ROS, a significant reduction in GSH level, and elevation of cysteine sulfenylation. STAT3, a transcription factor involved in the regulation of TH17-related genes, was the primary target of sulforaphane-mediated protein oxidation. Sulforaphane consequently attenuated IL-22, IL-17A, and IL-17F (TH17-related cytokines) and transcription factor RORgt expression, which are primarily involved in numerous chronic inflammatory diseases pathophysiology. Sulforaphane also inhibited the activation of untransformed human T-cells derived from RA patients or healthy donors. N-acetylcysteine, an antioxidant that replenishes GSH and administers GSH exogenously, reversed the inhibitory effects of sulforaphane. Liang et al. (2018) provided mechanistic insights into the mechanism of action of sulforaphane. By reducing GSH and increasing ROS, it specifically has immunosuppressive effects on human T-cells that have not undergone transformation. The strong inhibitory effect of sulforaphane on human T-cells activation obtained from RA patients indicated that it might have potential for development into an antirheumatic agent activation in vitro and in vivo studies.

4.1.16 | Tetrandrine

Tetrandrine, an alkaloid extracted from the Chinese botanical Han-Fang Chi, which is used in TCM to treat rheumatic diseases, hypertension and silicosis. Ho et al. (2004) reported that the alkaloid effectively inhibited cytokine proliferation and production capabilities of CD28-stimulated T-cells. They examined how NF-κB transcription factors, which are essential for CD28 co-stimulation, could influence tetrandrine-activated immunosuppression in human peripheral blood T-cells. They demonstrated tetrandrine suppressed the DNA-binding capabilities of NF-κB, which were activated by various stimuli, including CD28 co-stimulation. At equivalent molar concentrations, tetrandrine was as efficacious as methotrexate at inhibiting CD28-stimulated NF-κB activity. Tetrandrine might regulate NF-κB upstream signaling molecules, as tetrandrine did not affect NF-κB's binding to its corresponding genomic sequence. Subsequent research revealed that tetrandrine might impede the nuclear translocation of p65 and inhibited IkBα kinase α and β activity by degrading IκBα. Moreover, tetrandrine inhibited the activation of MAPKs, including p38, JNK, and extracellular signal-regulated kinase, as well as the DNA-binding ability of activator protein-1. Tetrandrine inhibited the transcriptional activity of NF-κB. Human peripheral blood T-cells were transfected to confirm this effect. These results laid the molecular foundation for tetrandrine's potential as a disease-modifying antirheumatic medication for the treatment of autoimmune diseases such as RA.

4.1.17 | Rosmarinic acid

The anti-arthritic activity of rosmarinic acid, a phenolic compound and ester of caffeic acid isolated from the butanol fraction of *Punica*

granatum rind in FCA-treated arthritic rodents, was evaluated by Gautam et al. (2019). Rosmarinic acid at 25 and 50 mg/kg significantly reduced the paw volume, arthritic score, joint diameter, white blood cell count, and erythrocyte sedimentation rate. Additionally, body weight, hemoglobin, and red blood cell counts were significantly increased., The treated groups showed significantly lower levels ($p < 0.001$) of TNF-α as compared to the rats with arthritis in the control group. MDA levels were significantly reduced, while antioxidant parameters (such as GSH and SOD) were increased at the same time ($p < 0.001$). These findings revealed that rosmarinic acid has a significant anti-arthritic potential as it could reduce the severity of arthritis in the FCA-treated arthritic rodents.

4.1.18 | Curcumin

Curcumin, which is primarily extracted from the rhizomes of various *Curcuma* species, has been extensively investigated for its anti-inflammatory and immunosuppressive activities. Surh et al. (2001) demonstrated that curcumin inhibited NO, iNOS, COX-2, and NF-κB and lipoxygenase in TNF-α or IFN-γ-stimulated NK cells and macrophages. Cianciulli et al. (2016) reported that pretreatment of LPS-stimulated microglial cells with curcumin significantly suppressed NO production, the expression and release of IL-6, IL-1β, TNF-α, NF-κB activation, PI3K/Akt phosphorylation, and iNOS expression. In another study, curcumin also attenuated TNF-α, NO and PGE_2 production, and COX-2 and iNOS expression in LTA-stimulated microglial cells (Yu et al., 2018). In vivo studies to determine the anti-inflammatory and immunosuppressive effects of curcumin were performed with several animal models. Wang et al. (2019) reported that 200 mg/kg of curcumin suppressed arthritis and averted the histopathological in rodents infected with CIA. It also substantially inhibited pro-inflammatory cytokine (IL-17, TNF-α, TGF-β, and IL-1β) production, white blood cell count in the synovium at the same dose. In another study, curcumin reduced Th17, Th2, and Th1 levels and slightly elevated Treg percentages in pristane-induced lupus mice (Alambra et al., 2012). Extensive clinical studies are ongoing on its anti-inflammatory properties, including for treatment of RA, and the current status can be accessed at http://www.clinicaltrials.gov/ (Jantan et al., 2015).

4.1.19 | Quercetin

Quercetin, a significant flavonoid compound present in numerous edible plants, has also demonstrated RA-alleviating potential. It has been reported that quercetin was effective in treating RA in rodents by preventing neutrophil infiltration. Quercetin decreased the levels of TNF-α, IL-6, IL-4, and INF-γ. This study also found that quercetin inhibited the production of neutrophil extracellular traps (NETs), an inflammatory marker (Yuan et al., 2020). In addition, nano-emulsion gel containing quercetin demonstrated anti-RA activity. Using the CFA model, a topical gel dosage form containing quercetin significantly reduced paw volume and joint inflammation severity in CFA rats. Quercetin in nano-emulsion gel reduced the production of pro-inflammatory cytokines including TNF-α (Gokhale et al., 2019). The ability of quercetin and in its nano-emulsion form to alleviate RA severity in CFA rats indicated that it could be developed into a therapeutic agent for the treatment of inflammatory conditions, such as RA.

4.1.20 | Rutin

Rutin, a flavonoid found in numerous foods such as grapes, oranges, cherries, and apricots, has been investigated for its anti-inflammatory effect in a RA experimental model. Using a CFA rat model, the anti-rheumatoid arthritis effect of rutin and rutin-conjugated gold nanoparticles was evaluated. In this study, bovine type-II collagen-induced RA. Upon intraperitoneal administration of rutin (50 mg/kg) for 22 days, it was discovered that rutin substantially decreased the severity of arthritis as well as NO and peroxide levels compared with the negative control. Rutin attenuated NF-κB and iNOS expression in the treatment group. In addition, rutin-conjugated gold nanoparticles reduced oxidative stress markers level and NF-κB and iNOS expression in a rat model of RA (Gul et al., 2018). The anti-RA effect of rutin and its gold nanoparticles in RA rat model highlighted rutin as a potential candidate for further development into anti-arthritic agent.

4.1.21 | Resveratrol

Resveratrol (trans-3,5,4′-trihydroxystilbene) is a flavonoid that is widely distributed in fruits and vegetables. Yang et al. (2018) reported the anti-RA efficacy of resveratrol. Rat RA was induced utilizing bovine type-II collagen (BIIC). The 400 mg/kg bw dose of resveratrol prevented the change in histological parameter and lowered the severity of arthritis. It was discovered that resveratrol substantially decreased the production of oxidative stress as well as TNF-α, IL-6, IL-1β, and MCP-1 in BIIC rats compared with rats receiving a placebo. In the rodent model of RA, resveratrol demonstrated antioxidative and anti-inflammatory properties. The significant anti-RA effect in lowering the severity of arthritis in BIIC-induced rats indicated that resveratrol has potential for further development into an anti-arthritic agent.

4.1.22 | Salicin

Salicin, an alcoholic β-glucoside isolated from *Alangium chinense*, was evaluated for its anti-RA activity by evaluating its effects and putative mechanism on inflammation and oxidative stress in RA fibroblast-like synoviocytes (RA-FLSs). Salicin inhibited the oxidative damage indexes of ankle joinT-cells and substantially suppressed the CIA in vivo by diminishing the clinical score, inflammatory infiltration, and synovial hyperplasia. Salicin inhibited RA, which may be related to

oxidative stress and Nrf2-HO-1-ROS pathways in RA-FLSs (Zhai et al., 2018). Salicin could be a potential candidate for further development as an anti-inflammatory agent for treatment of RA due to its strong inhibitory effect against inflammation and oxidative stress in RA-FLSs.

4.1.23 | α-Mangostin

The anti-arthritis effect of α-mangostin, a major xanthone from the pericarp of *Garcinia mangostana*, was investigated by using adjuvant-induced arthritis (AA) rats. As an adjuvant, inactivated BCG was used to induce arthritis in the animal model. This adjuvant exacerbated inflammation and cytokine production, leading to the development of RA. α-Mangostin appeared to have the potential to reduce the severity of RA. α-Mangostin at 40 mg/kg ameliorated the severity of arthritis in rats and significantly decreased paw oedema. The profile of pro-inflammatory cytokines and immune homeostasis in AA rat joints were also altered by α-mangostin. Compared with the negative control, α-mangostin decreased the secretion of IL-1β and TNF-α significantly. This result indicated that α-mangostin might safeguard the joint by reducing endogenous pathogenic factors and regulating immune homeostasis (Zuo et al., 2018). The ability of α-mangostin to significantly reduce the severity of RA in AA rats indicated its potential for further development into an anti-arthritic agent for the treatment of RA.

4.1.24 | Rosmanol and carnosol

Two phenolic terpenoids, rosmanol and carnosol, isolated from *Callicarpa longissima* (Hemsl.) Merr. reduced RA symptoms in rodents with type-II collagen-induced arthritis and inhibited pro-inflammatory cytokines (TNF-α, MCP-1, and IL-6). As measured by the arthritis index score on day 42, the treatment with of rosmanol and carnosol (40 mg/kg each) significantly reduced the severity of RA. In addition, they prevented p38 MAPK and TLR4/NF-B/JNK pathways activation. Surprisingly, the combination of rosmanol and carnosol (20 mg/kg/d each) significantly increased the inhibition of these pathways. In CIA DBA/1 mice, carnosol and rosmanol had a synergistic effect on relieving RA (Li et al., 2022). In another study, 14 days of carnosol treatment (50 mg/kg) suppressed lymphocyte infiltration, thereby alleviating CIA in rodents. The differentiation of Th17 cells in the CIA model was suppressed by carnosol. In accordance with the decrease in Th17 frequency, the mRNA level of IL-17A in carnosol-treated joint tissues was significantly lower than in the vehicle group. Carnosol was also able to stabilize the activity of Treg cells. CD4 + CD25 + IL-17A plus After 3 days of stimulation with recombinant murine IL-6 (rmIL-6), the number of Treg cells in the carnosol-treated group was significantly lower than in corresponding groups. The results indicated that conversion of Treg cells to Th17 cells was prevented by carnosol, which might sustain their suppressive function in CIA inflammatory environment (Chen et al., 2023). Both compounds have good potential to be further investigated as an anti-arthritic agent for clinical use to heal RA patients as they significantly reduced the severity of RA in CIA mice.

4.1.25 | Mangiferin and glycyrrhizic acid

Mangiferin, a major C-glucosyl xanthone of *Mangifera indica* L., showed anti-inflammatory activity through the suppression of TNF-α expression at 10 μg/mL (Brito et al., 2019). The outcome of this study was further supported by *in silico* docking study as reported by Somani et al. (2016), which indicated that mangiferin showed strong binding affinity value of −8.4 kcal/mol. According to Samadarsi et al. (2022), mangiferin exhibited high binding affinity (−8.0 to −7.6 kcal/mol) for TNF-α. The combination of mangiferin and glycyrrhizic acid inhibited the adjuvant-induced arthritis (AIA) rodent model of RA. Mao et al. (2022) reported that the combination enhanced their ability to diminish the severity of RA in rodents with AIA. The combination also decreased the production of pro-inflammatory cytokines and oxidative stress. The study was then confirmed using an in silico model, in which their anti-arthritic effect may be due to reversing the disturbance of thermogenesis as well as energy metabolism. The outcomes of these studies, specifically the significant effect of mangiferin and glycyrrhizic acid combination in inhibiting AIA in RA rodent highlighted the potential of their usage in the treatment of RA.

4.1.26 | Taraxasterol

Triterpenoids have diverse pharmacological properties, including anti-inflammatory properties. The medicinal plant *Taraxacum officinale* contains several bioactive compounds, including taraxasterol. Chen et al. (2019) studied the anti-RA activity of taraxasterol in mice using CIA. They reported that 10 mg/kg bw of taraxasterol could reduce collagen-induced arthritis. Taraxasterol also prevented synovial inflammation in CIA mice and suppressed pro-inflammatory cytokine production in animal model joint tissues by modulating the activation of NF-κB and NLRP3 inflammasome pathways (Chen et al., 2019). The articular cartilage lesions were reversed by 5 and 10 mg/kg of taraxasterol. Taraxasterol downregulated the the NF-κB signaling pathway and expression of serum inflammatory mediators such as IL-6, TNF-α, and IL-1. In rats induced by papain and cysteine, the inflammatory response-related genes LBP, A2M, S100A8, CCR1, and CCL3 were also decreased by taraxasterol (Xie et al., 2022). Taraxasterol inhibited inflammation in osteoarthritis rat model by regulating miRNAs and NF-κB signaling pathway. This study was in agreement with a study by Jiang et al. (2016) which reported that taraxasterol was able to prevent RA by modulating inflammatory response in mice, these include suppressing TNF-α, IL-1β, IL-6, NO, and PGE_2 levels as well as NF-κB and COX-2 expression levels. The anti-inflammatory effect of taraxasterol in osteoarthritis rat model suggested that it has good potential to be further investigated as an anti-arthritic agent for clinical management of RA.

4.1.27 | Stigmasterol

Ahmad Khan et al. (2020) reported the effectiveness of stigmasterol, a phytosterol abundant in a variety of plant kingdoms, in inhibiting RA in an animal model. Stigmasterol exhibited anti-arthritic activity in collagen type-II (CII)-induced arthritis rats. At 200 mg/kg bw, stigmasterol alleviated inflammation and arthritic index. In addition, stigmasterol attenuated pro-inflammatory cytokines production by decreasing the NF-κB mRNA level. Evaluation of the expression of inflammatory proteins such as p-IKB, iNOS, and COX-2 also confirmed stigmasterol's anti-arthritis activity. The result showed that stigmasterol exhibited anti-arthritic activity in CII-induced arthritis rats by significantly inhibiting the expression of the proteins in joint tissue, thus suggesting its potential for further studies as an anti-arthritic agent.

4.1.28 | Ursolic acid

Ursolic acid, a pentacylic triterpenoid present in many plants, including peppermint, apple, prunes, lavender, and thyme, has been reported for its anti-inflammatory and anti-arthritic properties. Ahmad et al. (2018) reported that ursolic acid-rich extract could suppress RA in CFA rats by inhibiting COX 1 and 2 activation and reducing pro-inflammatory cytokines (such as TNF- and IL-1) production. Ursolic acid ameliorated osteoarthritis due to its anti-inflammatory effect via modulation of the NF-κB/NLRP3 inflammasome network (Wang et al., 2020). The preservation of white and red pulps by ursolic acid correlates with a high rate of proliferation of splenic mononuclear cells, IFN-γ mRNA and iNOS production (Jesus et al., 2017). By inhibiting MAPKs, IL-6/STAT3, and PI3K, ursolic acid treatment inhibited three classical inflammatory pathways. The proportion of macrophages and neutrophils in inflammatory cell infiltration was reduced in ursolic acid treatment groups (Sheng et al., 2021). The ability of ursolic acid to suppress RA in CFA rats through inhibition of the three classical inflammatory pathways suggested that it has good potential for further development into an anti-arthritic agent for treatment of RA.

4.1.29 | Cedrol

Cedrol, a sesquiterpene alcohol found in the essential oils of many aromatic plants such as *Juniperus* species and *Coniferous* species, was determined for its anti-nociceptive and anti-arthritic activities in a complete CFA rat model (Forouzanfar et al., 2022) They discovered that the compound significantly reduced the arthritic level in the animal model at a dose of 20 mg/kg as compared with the negative control. Anti-arthritis activity of cedrol was associated with anti-inflammatory activity, inhibiting the release of cytokines and joint oxidative stress production. Thus, cedrol has potential to be developed into an anti-arthritic agent for treatment of RA.

4.1.30 | Theaflavin-3,3′-digallate

Zhang et al. (2023) examined the in vivo anti-arthritic activity of theaflavin-3,3′-digallate, a polyphenol found in black tea. In this investigation, DBA/1 rodents were injected with Freund's adjuvant for 8–10 weeks to induce arthritis. The animal was then administered varied doses of the substance. Compared with untreated animals, theaflavin-3,3′-digallate at 10 mg/kg significantly reduced joint degeneration. This compound also suppressed the secretion of TNF-α, IL-6, IL-1β, and pro-inflammatory M1 macrophages. The strong anti-arthritic activity of this polyphenol in Freund's induced arthritis rodents should encourage further studies to evaluate its potential as an anti-arthritic agent for treatment of RA.

4.1.31 | Zerumbone

Zerumbone, a natural monocyclic triterpenoid of the rhizome of *Zingiber zerumbet* has been much investigated for its anti-inflammatory and immunosuppressive activities. Zerumbone blocked the secretion of pro-inflammatory cytokines such as IL-1β and TNF-α, PGE2, and COX-2 in LPS-stimulated human macrophages. Zerumbone also considerably suppressed phosphorylation of NF-κB (p65), IκBα, and IKKα/β and restored IκBα degradation. The compound also significantly and dose-dependently inhibited the expression of ERK, JNK, p38 MAPKs, and Akt. Zerumbone downregulated the activation of TRL4 and MyD88 via suppression of PI3K-Akt, MAPKs, and NF-κB pathways. At 50 μM, zerumbone significantly decreased the TNF-α, IL-1β, and COX-2 relative gene expression. The compound significantly suppressed the elevated mRNA transcription rate in LPS-activated U937 macrophages (Haque et al., 2018). Zerumbone at 5 and 10 mg/kg administered for 20 days in a CFA rat model exhibited significant reduction in the arthritic index and foot oedema when compared with the control. Zerumbone demonstrated a marked reduction in the profile of oxidative stress markers in tissue, including lipid peroxidase, SOD, and hydrogen peroxide. Similarly, zerumbone inhibited the secretion of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β in animal serum. According to the findings of this study, zerumbone exhibited anti-RA properties by modulating the release of cytokines and oxidative stress (Alsaffar et al., 2023). Zerumbone is a good drug candidate for developing into an effective and safe therapeutic agent for inflammatory and mediated immune disorders such as RA due to its anti-RA properties and strong anti-inflammatory and immunosuppressive effects in in vitro and in vivo studies.

4.1.32 | Pipernigramide and piperin

Amide alkaloids, namely, pipernigramide E, F, and G from *Piper nigrum* L., exhibited anti-inflammatory activity by inhibiting production of NO in LPS-activated RAW 264.7 cells (Xu et al., 2023). Piperine, another

primary component of *P. nigrum*, demonstrated anti-inflammatory activity by inhibiting COX-2 expression (Bang et al., 2009). This result was further substantiated by Chy et al.'s (2020) in silico docking simulation, which revealed that piperine exhibited a robust binding affinity value of −8.88 kcal/mol with the COX-2 protein. Moreover, absorption, distribution, metabolism, and elimination (ADME) analysis and toxicological property predictions indicated that piperine and piperlonguminine have excellent oral bioavailability and safety characteristics. These amine alkaloids can be selected as promising candidates for further experimental and preclinical studies on their effects in RA-infected animal models.

4.1.33 | Naringenin

Naringenin, a flavanone, is mainly found in tomatoes and citrus fruits. The nano-crystallization of naringenin enhanced its anti-inflammatory properties. The increasing efficacy of nanocrystals may be attributable to their high bioavailability, as indicated by their superior solubility, increased cellular absorption, and enhanced transcellular diffusion in comparison with bulk naringenin. In rodents with collagen-induced arthritis, naringenin nanocrystals effectively reduced inflammatory cell infiltration and synovial injury, thereby enhancing RA treatment (Zhang et al., 2021). Moreover, in acute and chronic animal models of RA, a liposomal formulation containing naringin in combination with isothiocyanates exhibited anti-inflammatory effects. Liposomal naringenin and phenethyl isothiocyanate (375 + 375 g/mL) improved paw oedema and arthritic score in FCA rats in comparison with their free drug combinations when administered intraperitoneally for 3 weeks. Hematological and biochemical tests revealed significant alterations in SGOT, SGPT, and ALP levels, indicating an improvement in anemia. Liposomes containing naringenin and phenethyl isothiocyanate increased IL-10 (an anti-inflammatory cytokine) and decreased markers of inflammatory cytokines such as TNF-α, IL-6, and IFN-γ. The result was corroborated by microscopy, which revealed a decrease in pannus formation, bone and cartilage degradation, and cell infiltration, The enhanced anti-inflammatory effect of naringenin and phenethyl isothiocyanate combination in liposomal formulation might also be due to the increased bioavailability of the compound (Mohanty et al., 2020). The significant anti-inflammatory and immunosuppressive activities of naringenin in animal models of RA highlighted its potential as a good candidate for clinical development into an anti-arthritic agent for treatment of RA.

4.1.34 | Xanthohumol

The prenylated chalcone, xanthohumol, is the most abundant compound in *Humulus lupulus*. Micellar solubilization increased xanthohumol's anti-inflammatory effect. Micellar-solubilized xanthohumol at a dose of 5 mg/kg significantly decreased paw volume, with an activity comparable with that of diclofenac. Twenty days of treatment with micellar-solubilized xanthohumol decreased TNF-α, IL-6, CRP levels, and serum MPO. The native form of xanthohumol had no effect on oxidative stress and MPO (Khayyal et al., 2020). Furthermore, xanthohumol (10 mg/kg) injected intraperitoneally into mice for three consecutive days (15, 16, 17) after CIA injection reduced the number of spontaneous flinches and increased mechanical pain thresholds and latency time. In addition, xanthohumol treatment of the spinal cord reduced spinal inflammation, as indicated by a decrease in IL-1β and glial fibrillary acidic protein (GFAP) intensity. Xanthohumol also simulated the Nrf2-mediated antioxidant response and decreased the level of mitochondrial ROS and NLRP3 inflammasome-mediated inflammation. Molecular docking revealed that xanthohumol interacts with AMPK via two electrovalent bonds and increases AMPK phosphorylation at Thr174 (Wang et al., 2023). According to a previous study, xanthohumol has the ability to reduce inflammation in chondrocytes and ameliorated osteoarthritis in mice. After IL-1 stimulation, chondrocytes incubated with xanthohumol at concentrations of 10, 25, and 50 μM inhibited the elevation of PGE2, IL-6, NO, and TNF-α. Decreased expression of matrix metalloproteinase-13 and increased expression of type-II collagen and aggrecan suggested that xanthohumol delayed the degradation of osteoarthritis chondrocytes in mice. Furthermore, xanthohumol activated Nrf2 in IL-1β-stimulated chondrocytes and inhibited NF-κB signal transduction (Chen et al., 2021). The strong anti-inflammatory and anti-osteoarthritis effects of xanthohumol in these in vivo studies suggested that it is a potential candidate for clinical studies for development into an anti-arthritic agent to treat RA.

4.1.35 | Cannabidiol

Cannabidiol, a phytocannabinoid is one of the major constituents of *Cannabis sativum* L., and has been reported to inhibit the secretion of inflammatory mediators and reduced the arthritic score in collagen-induced arthritic rats on its oral administration (Malfait et al., 2000). Cannabidiol given orally at concentrations of 10, 25, and 50 mg/kg to CIA-infected mice for 10 days prevented the progression of arthritis. Cannabidiol at a dose of 25 mg/kg protected joints from severe injury most effectively. In addition, intraperitoneal administration of cannabidiol at concentrations of 20, 10, 5, and 2.5 mg/kg was able to inhibit the progression of arthritis, with the optimal effect occurring at 5 mg/kg. Five weeks of chronic cannabidiol treatment in an identical CIA model yielded comparable outcomes. Cannabidiol treatment inhibited synovial cell-derived TNF-α production, lymph node culture proliferation, and IFN-γ production. Additionally, cannabidiol inhibited Con A-induced lymphocyte proliferation. Similar results were observed following the induction of bovine type-II collagen. Cannabidiol inhibited ROS production from granulocytes stimulated by zymosan and the production of TNF-α in mice activated by LPS (Malfait et al., 2000). Hammell et al. (2016) reported the ability of transdermal cannabidiol gel to reduce inflammation and pain. Application of 6.2 or 62.3 mg/day of cannabidiol gel for four consecutive days suppressed joint oedema, synovial membrane thickening, limb posture scores, and immune cell infiltration, as a rating of spontaneous pain. There were

dose-dependent reductions of the pro-inflammatory biomarkers calcitonin gene-related protein and oxyacanthine-related protein as revealed by immunohistochemical analysis of the dorsal root ganglia and spinal cord. The strong attenuation effect of cannabidiol on inflammatory mediators' secretion and reduction of the arthritic score in CIA rats might suggest that it has potential for clinical studies for development into an anti-arthritic agent for treatment of RA.

4.1.36 | Licochalcone A

Licochalcone A (LCA), a chalconoid derived from the roots of *Glycyrrhiza inflata*, has many pharmacological activities including anti-inflammatory activity. LCA exhibited strong anti-arthritis effect in the CIA model of DBA mice through stimulation of SQSTM1 (p62)/Nrf2 signaling network. However, the anti-arthritic effect of LCA was remarkably reduced in the collagen antibody-induced arthritis (CAIA) model of Nrf2 mice. In an in vitro study, the anti-arthritis effect of LCA was determined in RA synovial fibroblasts (RASFs) isolated from the synovium of RA patients. It was observed that LCA inhibited secretion of pro-inflammatory cytokines and upregulated antioxidant enzyme expression through Keap1-Nrf2 signaling activation by stimulating phosphorylation and expression of p62, accumulation of Nrf2, and translocation of Nrf2 nucleus (Su et al., 2018). The ability of LCA to interfere with the interaction between Keap1 and Nrf2 by phosphorylation of p62 may be a promising strategy for the discovery of anti-arthritic agents. The ability of LCA to interfere with the interaction between Keap1 and Nrf2 by phosphorylation of p62 may be a promising strategy for the discovery of anti-arthritic agents.

4.1.37 | Carvacrol

Carvacrol, a phenolic monoterpenoid, can be found in the essential oils of numerous plants, including thyme (*Thymus vulgaris*), oregano (*Origanum vulgaris*), wild bergamot (*Citrus aurantium bergamia*), and pepperwort (*Lepidium flavum*). Carvacrol inhibited secretion of TNF-α, IL-6, and IL-8 and prevented the activation of the TLR4/MyD88/NF-κB, p38, and ERK1/2 pathways in LPS-induced RA-FLSs (Li et al., 2019). Gholijani et al. (2020) demonstrated the anti-inflammatory effect of carvacrol-loaded bovine serum albumin (BSA) nanoparticles on arthritic rats, which supported the therapeutic effect of carvacrol. Compared with the untreated arthritic group, administration of carvacrol-loaded BSA nanoparticles intraperitoneally every 3 days until day 28 significantly decreased clinical severity score, erythrocyte sedimentation rate, NO production, and IL-17 gene expression. Surprisingly, carvacrol combined with thermal duress could stimulate mouse tolerogenic dendritic cells (Spiering et al., 2012). Further in vivo and preclinical studies to evaluate the anti-inflammatory and anti-arthritic activities of carvacrol are required prior to clinical study for its development into a therapeutic agent to treat RA.

4.1.38 | Perillyl alcohol

Perillyl alcohol (POH), a monoterpene obtained from the essential oils of several plants, including citronella, lavender, peppermint, spearmint, and celery seeds, has been reported for its strong anti-oxidant and anti-inflammatory activities. The anti-arthritic activity of POH in in vitro and in vivo experimental models was assessed by Puppala et al. (2022). POH demonstrated inhibitory activity by reducing the levels of pro-inflammatory cytokine (TNF-α, IL-6, and IL-1β), COX-2 and PGE_2 levels, ROS production, nitrate levels, and Nrf2 and NF-κB signaling in RAW 264.7 cells treated with LPS (1 μg/mL). Topical administration of POH at 100 and 200 mg/kg from day 1 to day 28 could effectively reduce CFA-induced inflammation in rats. POH significantly reduced paw volumes, joint inflammation, pannus formation, and bone erosion, besides reducing the pro-inflammatory cytokine levels. It was also observed that POH downregulated the protein expressions of COX-2, iNOS and NF-κB and increased the levels of superoxide dismutase 2 (SOD2) and Nrf2 in the paw tissues. The findings indicated that POH has potential to be developed into an anti-arthritic agent as it exhibited in vitro and in vivo anti-arthritic effects by modulating the TLR4/NF-κB and Keap1/Nrf2 signaling networks.

4.2 | Clinical trials

Many of the phytochemicals investigated for their in vitro and in vivo anti-inflammatory and immunosuppressive activities with therapeutic potential for RA including sinomenine, resveratrol, naringenin, xanthohumol, cannabidiol, and β-D-Mannuronic acid have been subjected to clinical studies. However, most clinical studies have some limitations, such as relatively small sample size, short duration of the studies, and lack of a placebo group. Further high-quality studies are needed to firmly establish the clinical efficacy of the phytochemicals. Before developing anti-inflammatory drugs for treating RA, it is crucial to conduct thorough clinical investigations in phases 1, 2, and 3.

4.2.1 | Sinomenine

A randomised, controlled trial was carried out to investigate the effects of sinomenine on RA patients. A total of 49 participants were administered sinomenine at a dosage of 60–120 mg, twice daily. The results indicated that sinomenine treatment led to the suppression of many pro-inflammatory cytokines, including TNF-α, IL-1β, IL-1α, and IL-6. Sinomenine was found to enhance the secretion of IL-10, which is an anti-inflammatory cytokine. Additionally, sinomenine reduced the percentage of CD14 + CD16+ in PBMCs of RA patients (Liu et al., 2018).

4.2.2 | Resveratrol

The effects of resveratrol supplementation on IL-1β and IL-6 in outpatients with New York Heart Association class II-III heart failure and

reduced ejection fraction were investigated. The study was single-centered, double-blind, randomized, and placebo-controlled. Sixty individuals were enlisted in the research and given 100 mg of resveratrol per day for 3 months. The results showed a significant decrease in IL-1β and IL-6 levels following resveratrol supplementation (Gal et al., 2021).

4.2.3 | Naringenin

A total of 180 eligible patients (naringenin and azithromycin groups) were involved in a randomized controlled trial in children with bronchial pneumonia. All participants requested to follow a 5-day oral administration of naringenin with a daily dosage of 5 mg/kg was able to inhibit inflammation by reducing the level of IL-6, IL-8, and TNF-α and increasing the anti-inflammatory cytokine IL-10 (Yao et al., 2021).

4.2.4 | Xanthohumol

In a single-blind, cross-over, and placebo-controlled clinical study, 14 healthy volunteers ingested either a placebo or a beverage containing 0.125 mg of xanthohumol. PBMCs isolated 1 h after drinking the beverages, were then induced with lipoteichoic acid (LTA) for 24 and 48 h. The LTA-dependent induction of release of sCD14, IL-6, and IL-1β proteins from PBMCs was not significantly greater than in unstimulated cells after 48 h of ingestion of xanthohumol (Jung et al., 2022).

4.2.5 | Cannabidiol

In a preliminary pilot double-blind study, randomized, and parallel limb involving 10 healthy volunteers, a single 30-mg dose of cannabidiol was administered, which falls within the range of typical commercial supplement doses. PBMCs were extracted from the samples after 90 min, cultured, and stimulated with LPS, and the study demonstrated a decrease in TNF-α secretion (Hobbs et al., 2020).

4.2.6 | β-D-Mannuronic acid

β-D-Mannuronic acid, a homopolysaccharide, is derived from brown marine phytoplankton or seaweed. In a clinical trial involving 12 RA patients and 12 healthy individuals, the miR-155 gene expression level in the β-D-mannuronic acid-treated patients was significantly lower than at baseline. In addition, the expression levels of the SOCS1 and SHIP1 genes were significantly higher in β-D-mannuronic acid-treated patients than they were before treatment. The study also exhibited a significant decrease in NF-κB expression in β-D-mannuronic acid-treated patients as compared with the baseline (Mortazavi-Jahromi et al., 2020). In another study, the potential effect of 1000 mg of β-D-mannuronic acid (M2000) per day for 12 weeks in RA patients was investigated. After 12 weeks of treatment with M2000, gene expression of chemokine receptors and ligands, including CXCR4, CCR2, and CCL2/MCP-1, decreased significantly as compared with before treatment. The patient receiving M2000 for 12 weeks reduced inflammatory reactions, such as pain and morning rigidity (Aslani et al., 2020). Barati et al. (2017) demonstrated that M2000 could be used as a rheumatoid therapy agent due to a number of its pharmacological effects, such as the regulation of rheumatoid factor, C-creative protein, IL17, and RORγt gene expressions near to normal range (22.39- and 2.36-fold, respectively) during 12 weeks of therapy with M2000 capsules (500 mg twice daily). In contrast, the parameters of IL4 and GATA3 gene expression in PBMCs of patients increased by 0.92 and 0.48-fold, respectively, in comparison with before treatment.

Conclusively, there are some sites of action of plant bioactive compounds. Figure 1 shows that triptolide inhibited MMPs released by FLS, thus inhibiting breakdown of cartilage and joint. Pannus formation was inhibited by pristimerin dan celastrol. Stemucronatoside and periplocoside E blocked the release of IFNγ. The mechanism of action of various compounds in treating RA is shown in Figure 1 and Table 1.

5 | CONCLUSION

There is no permanent cure for RA. NSAIDs, DMARDs, and biologic agents are some of the therapeutics available as standard treatments to help reduce symptoms such as inflammation, pain, stiffness, and bone loss in people with RA, but they usually cause significant side effects and are not always effective. Plant extracts and their secondary metabolites have been used for generations to treat diverse immune and inflammatory-related diseases, such as RA. A wide range of phytochemicals including phenols, flavonoids, chalcones, xanthones, terpenoids, alkaloids, and glycosides have been investigated in experimental studies for their potential to treat RA due to their anti-inflammatory and immunosuppressive activities. Preliminary clinical studies have also been performed on some of them. These plant secondary metabolites have potential to be developed into safer and more effective alternatives to the currently used anti-inflammatory and immunosuppressant drugs. However, at present, research into these compounds is too preliminary to make specific recommendations, and some of them may interact with the traditional treatments. More studies are needed to fully understand their mechanisms of action and potential side effects. Sufficient preclinical studies on safety and efficacy of these phytochemicals must be performed prior to proper clinical studies. Clinical trials are needed to establish the efficacy and safety of the plant-based substances in the management of RA. Thus, understanding the mechanisms of actions involved in the anti-inflammatory and immunosuppressive effects of plant secondary metabolites in association to RA will provide useful information for their development into agents for prevention and treatment of RA.

AUTHOR CONTRIBUTIONS

Yuandani: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; software; validation; visualization; writing-original draft. **Ibrahim Jantan:** Conceptualization; data curation; methodology; supervision; writing-review and editing. **Emil Salim:** Data curation; methodology; writing-review and editing. **Abdi Wira Septama:** Software; supervision; visualization; writing-review and editing. **Kamal Rullah**; **Firzan Nainu**; **Mohd Fadhlizil Fasihi Mohd Aluwi:** Conceptualization; data curation; methodology; writing-review and editing. **Talhah bin Emran:** Methodology; writing-review and editing. **Miah Roney**; **Muh. Fadhil As'ad:** Visualization, writing-review and editing. **Nur Aini Khairunnisa**; **Halimah Raina Nasution: Nur Farisya Shamsudin**; **Maryam Aisyah Abdullah:** Data curation; writing-review and editing. **Haya Luthfiyyah Marwa Rani**; **Diany Mahabbah Al Chaira**; **Nabila Aulia:** Data curation.

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CONFLICT OF INTEREST STATEMENT

The authors declare there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

None.

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