Molecular Biology Reports (2024) 51:448
https://doi.org/10.1007/s11033-024-09386-9

REVIEW

Pharmacological and immunomodulatory modes of action of medically important phytochemicals against arthritis: A molecular insight

Aqsa[1] · Shaukat Ali[1] · Muhammad Summer[1] · Saima Yousaf[2] · Laiba Nazakat[1] · Shehzeen Noor[1]

Received: 26 January 2024 / Accepted: 26 February 2024

Abstract

Arthritis is a common illness that affects joints and it may result in inflammation and pain. Even though arthritis usually affects older people, it can also affect children, adults, and both genders. Numerous arthritic mouse models have been developed but the CIA model of rheumatoid arthritis (RA) has received the most attention. With the use of steroids, DMARDs, and NSAIDs, therapy objectives such as reduced disease incidence and better pain management are achieved. Long-term usage of these therapeutic approaches may have negative side effects. Herbal medications are the source of several medicinal substances. Studies have explored the potential benefits of medicinal plants in treating RA. These benefits include up-regulating antioxidant potential, inhibiting cartilage degradation, down-regulating inflammatory cytokines such as NF-kB, IL-6, and TNF-α, and suppressing oxidative stress. In this review, we systematically discuss the role of traditional medicinal plants in rheumatoid arthritis (RA) disease treatment. The role of different medicinal plants such as *Curcuma longa, Syzygium aromaticum, Zingiber officinale* and *Withania somnifera*, against arthritis is discussed in this review.

Keywords Rheumatoid arthritis · Medicinal plants · Mechanism · Phytochemicals

Abbreviations

AKBA	3-O-acetyl-11-keto-boswellic acid
CBP	Peptide that binds to collagen
CFA	Chartered Financial Analyst
CRP	C-reactive protein
CIA	Collagen-induced arthritis
CII	Collagen type II
COX	Enzyme cyclooxygenase
DCs	Dendritic cells
DMARDs	Disease-modifying anti-rheumatic drugs
ERK1/2	Extracellular signal-regulated protein kinases 1 and 2
FCA	Freund's Complete Adjuvant
HNE	4-hydroxy 2-nonenal
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL-1	Interleukin-1
IL-6	Interleukin-6
KBA	11-keto-boswellic acid
LPS	Lipopolysaccharide
MAPK	Mitogen-activated protein kinases
MHC	Major histocompatibility complex
MMPs	Matrix metalloproteinase
MTX	Methotrexate
MW	Molecular weight
NF-kB	Nuclear factor-kappa B
NK cells	Natural killer cells
NSAIDs	Non-steroidal anti-inflammatory agents
PGE2	Prostaglandin E2
RA	Rheumatoid arthritis
SCW	Streptococcal cell wall
SFs	Synovial fibroblasts

✉ Shaukat Ali
dr.shaukatali@gcu.edu.pk

[1] Medical Toxicology and Biochemistry Laboratory, Department of Zoology, Government College University, Lahore 54000, Pakistan

[2] Department of Zoology, Division of Science and Technology, University of Education, Lahore 54470, Pakistan

Published online: 27 March 2024

TCM	Traditional Chinese medicine
TGF	Transforming growth factor
THP-1	Tohoku Hospital Pediatrics-1(a cell culture of human-derived leukemia monocytic cells)
TNF-α	Tumor necrosis factor-alpha
TQ	Thymoquinone

Introduction

Musculoskeletal problems are the second most typical reason for body impairment, globally [1] and pose a danger to healthy aging [2]. The worldwide disability load linked to the musculoskeletal system is strongly impacted by arthritis [3]. More than 100 distinct arthritic conditions, which are agonizing, chronic, and a collection of disorders, are collectively referred to as "arthritis" [4]. An acute or chronic disease that affects one or more joints is also known as arthritis. Its clinical spectrum may include stiffness, discomfort, and joint abnormalities in addition to joint swelling [5]. It can also manifest in forms, such as osteoarthritis, psoriatic arthritis, and RA [6]. One of the most common chronic inflammatory illnesses is rheumatoid arthritis [7]. Symmetric polyarthritis, a symptom of rheumatoid arthritis that affects the synovial membrane and has been linked to high levels of IgM and IgA antibodies, is the disease's distinguishing feature [8]. Approximately 1% of people have rheumatoid arthritis (RA) all over the world, with men being less likely than women to develop it [9].

Rheumatoid arthritis mechanism of action

Genetic, environmental, and autoimmune variables are the key causes of RA's pathogenesis [10]. The main causes of RA in people with genetic susceptibility include smoking, hormones, infections, microbiome, and other variables [11]. Antigen-activated $CD4^+$ T cells are initiated by the different environmental and genetic variables causing the disease through the immune cells activation, such as synovial fibroblasts, macrophages, and monocytes [12]. TNF-α, Interleukin-6, and interleukin-1 are produced as a result of $CD4^+$ T-cell activation, which is the primary mediator of RA [13]. These pro-inflammatory mediators have a crucial role in the RA pathogenesis, including articular manifestation through inflammatory infiltration increase of cell types, mainly macrophages, B lymphocytes, T cells and bone erosion leading to the formation of autoantibodies and the release of Interleukin-6 and TNF-α as shown in Fig. 1 [14].

Autoimmune responses in rheumatoid arthritis cause macrophages and T cells to release inflammatory cytokines variety in the joints. This causes pain and swelling, ongoing bone and cartilage degradation, and systemic consequences over time that raise cardiovascular morbidity and mortality rates [15]. Additionally, these cytokines prevent collagen breakdown and proteoglycan production. Proteolytic enzyme activation like collagenases and MMPs causes cartilage degradation [16]. Additionally, certain protein molecules, such as cytokines and chemokines, cause synovitis and tissue damage by luring lymphocytes, monocytes, and neutrophils as well as the COX-2 enzyme. This tissue damage results in synovial joint hyperplasia and pannus formation that causes apoptosis in synovial fibroblasts [17]. The mechanism of RA within the joint capsule is also described below:

Since cartilage lacks blood vessels and nerves and is primarily made up of cartilage cells, extracellular matrix and fibers, it receives nutrition from blood vessels through the perichondrium via nutrient penetration into the intercellular substance [18]. Chondrocytes, the primary cartilage cells, control the homeostasis and cartilage's dynamic stability during catabolism and anabolism [19]. Any disruption of this equilibrium may cause damage to the cartilage tissue, which could result in arthritis. These internal and external causes may include inflammatory environments [20]. Immune cells such as natural killer (NK) cells, dendritic cells (DCs), macrophages, neutrophils, T lymphocytes, and B lymphocytes are the main producers of IL-1 as shown in Fig. 2 [21].

It is reported that the expression of the collagen type II (COL2A1) and chondrocyte-specific genes *Sox9* can be downregulated by IL-1, a process that may be sped up by T cells secreting IL-3 [22]. On the other hand, T cells' production of IL-6 and IL-3 protects the cartilage by preventing the development of MMPs through the use of tissue inhibitors. In some circumstances, IL-6 prevents the formation of proteoglycans in chondrocytes and increases IL-1 to cause proteoglycan denaturation [23]. IL-6, thus, plays an important role in protecting and destroying cells of cartilage, both of which are solely controlled by the immune system's reaction to allergens [24]. While transforming growth factor (TGF) is synthesized by T cells in comparison to other cells, and it promotes cartilage remodeling by down-regulating the expression of Interleukin-6 receptor in chondrocytes, thereby preserving the homeostasis of the cartilage and up-regulating the differentiation-related transcription gene *sox9* [25].

Although the specific origin of RA is still unknown, it is thought that the pathophysiology of RA is regulated by B cells, T cells, excess production of several proinflammatory cytokines, and dysregulation of anti-inflammatory cytokines [26]. Different animal models have been used to evaluate potential anti-arthritis drugs for clinical use. For

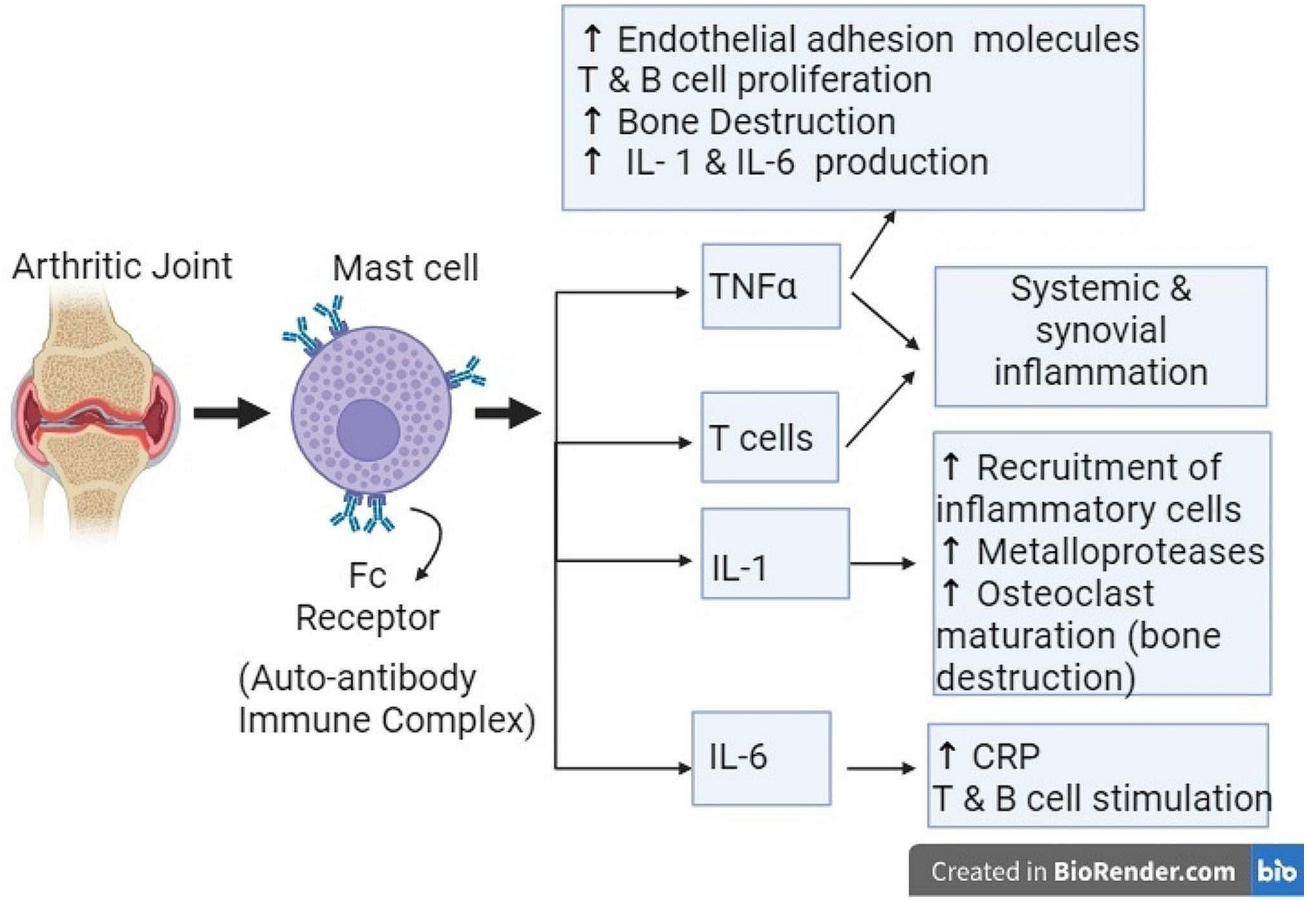

Fig. 1 Rheumatoid arthritis is caused by autoimmune reactions that cause macrophages and T cells to release a variety of inflammatory cytokines into the joints. This causes swelling and pain, gradually deteriorating bone and cartilage, and systemic consequences that eventually raise the risk of cardiovascular disease and death. The pathophysiology of RA is more complicated than is depicted in terms of the interactions between cytokines and other cell types

this purpose, collagen is widely used to induce arthritis in animal models.

Collagen-induced arthritis

Cartilage autoimmune response and the development of erosive polyarthritis were observed in rats that were immunized for the first time in 1977 with a chicken, rat, or human type II collagen (CII) emulsion in complete Freund's adjuvant (CFA) [27]. In 1986 and 1980, respectively, mice and monkeys were used to recreate this CIA model. A popular animal model for examining the effects of novel treatments for rheumatoid arthritis is collagen-induced arthritis. An injection of a collagen emulsion induces CIA [28], and with the antibody formation and activation of B-cell and T-cell activation, an immune response is initiated that targets collagen [29] The local autoimmune response is triggered when antibodies identify the collagen in the joints. Consequently, cytokines and other inflammatory mediators are produced [30].

Future expectations for RA prevention are shaped by the discovery of a preclinical stage, expanding knowledge of the natural history and mechanisms of RA development, and novel therapeutic approaches [31]. Different therapeutic approaches are described below.

Treatments of RA and complications associated with pharmacotherapy

Commonly, NSAIDs and steroidal anti-inflammatory drugs (corticosteroids) are used to reduce pain and inflammation in RA patients. Medication for RA includes B-cell depleting rituximab, IL-1 antagonist tocilizumab, TNF-blockers (etanercept, infliximab, adalimumab, and certolizumab), IL-6 antagonist tocilizumab, T-cell co-stimulator abatacept, and IL-1 receptor antagonist [32]. In addition, biological therapies and disease-modifying antirheumatic drugs (DMARDs) are used to reduce the progression of damage and to prevent the onset of illness [33]. Moreover, RA can be treated with other drugs including cyclosporine,

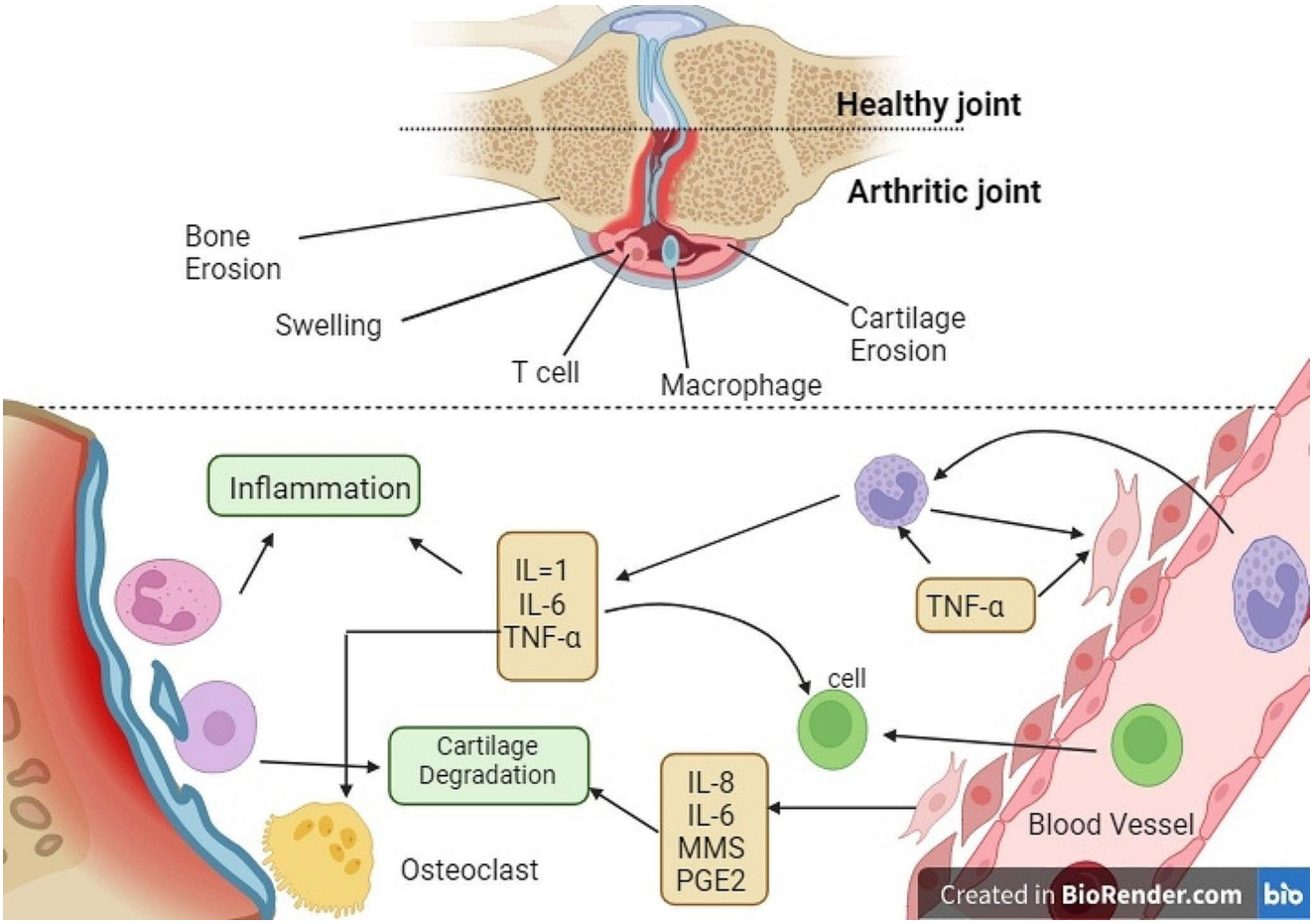

Fig. 2 Mechanism of RA within the joint capsule. TNF-α affects synoviocytes, monocytes/macrophages and osteoclasts; initiating RA pathogenesis. Synoviocytes line the capsule and T-cells infiltrate the synovial membrane, initiating inflammation via TNF-α. Joint degradation occurs via macrophage recruitment and secretion of inflammatory cytokines. Bone erosion occurs by osteoclasts and inhibition of collagen secretion by synoviocytes

minocycline, leflunomide, azathioprine, myochrysine, sulfasalazine, gold, hydroxychloroquine, and methotrexate [33, 34]. However, drugs used to treat arthritis may impact fertility and pregnancy. Using anti-rheumatoid medications like methotrexate, azathioprine, and cyclophosphamide to treat RA during pregnancy has proven to be a challenging approach. These medications can cause a number of potentially fatal teratogenic side effects, such as abnormalities in the developing fetus, problems with growth, and an increased risk of preterm birth. The focus of modern therapy has thus switched to herbal remedies that are complementary and alternative and have little adverse effects [35]. Several medicinal plants are used to make herbal medications. The active ingredients found in herbal plants, such as flavonoids, carotenoids, phenols, terpenes, and sesquiterpene lactones, are advantageous because they have anti-inflammatory and antioxidant properties. These characteristics make them a potent therapeutic strategy for the treatment of RA [34, 36].

Medicinal plants for rheumatoid arthritis treatment

Plant-based medications with the ability to control the expression of pro-inflammatory signals have the potential to treat arthritis [37]. Investigations into the anti-inflammatory properties of medicinal plant extracts have revealed a variety of mechanisms, some of which include blocking pro-inflammatory mediators [38].

Clinical studies have demonstrated the effectiveness of plant-derived alkaloids such as colchicines, isoquinoline, and aconitine as an arthritis treatment by lowering pain symptoms and inflammation [13]). The colchicines block neutrophil emigration, reduce activation of inflammasome and further reduce the levels of leukotriene and cytokines, which appear to be higher in arthritis characterized by chronic inflammation [39]. By inhibiting the enzyme cyclooxygenase (COX), the other alkaloids (indole, aconitine, and isoquinoline), terpenoids, and flavonoids demonstrate

antipyretic and analgesic effects by reducing inflammatory mediators and preventing joint degeneration [35].

Important mechanisms of natural medicines in the treatment of RA include reduction of the expression of inflammatory mediators, immunological regulation, inhibition of osteoclast development, anti-oxidative stress, and inhibition of proliferation and migration of FLSs. Fig. 3 summarizes the primary signaling pathways and transformation factors: PI3K/Akt, NF-kB, JAK2/STAT3 signaling, MAPK, AP-1, Nrf2, HIF-1α, and SIRT1 that are targeted by bioactive compounds of different medicinal plants used to treat RA.

When used in conjunction with MTX for the treatment of RA, several natural medications, including steroidal lactones, 8 shogaol, desmethoxycumin, curcumin, thymoquinone, eugenol and eugenol acetate, can produce greater therapeutic benefits and/or fewer side effects. These demonstrate in full the benefits of using natural medications to treat RA: they are safe, effective, natural, and have little harmful or adverse consequences [11, 40].

Curcuma longa

Originally from India, the perennial shrub *Curcuma longa*, a member of the Zingiberaceae family, is now grown in Sri Lanka, China, and other tropical countries [41]. Studies have revealed that curcuminoids including curcumin, desmethoxycurcumin, bisdemethoxycurcumin, monodemethoxycurcumin, dihydrocurcumin, and cyclocurcumin are present in turmeric, one of the plants that has been the subject of the most research [42]. The major ingredient in turmeric, curcumin, has drawn a lot of interest as a plant-based substance with pharmacological benefits that are pleiotropic. It has immunomodulatory, neuroprotective, hypoglycemic, antioxidant, anti-inflammatory, and antibacterial properties [43]. The pre-clinical experiment investigated how giving animals a low dose of *C. longa* extract prevented both the chronic and acute phases of arthritis and found that curcuminoid, the active element in *C. longa*, has potent anti-inflammatory activities [13].

By preventing the generation of pro-inflammatory cytokines including Interleukin-1, TNF-α and Interleukin-6, curcumin is successful in preventing the advancement of

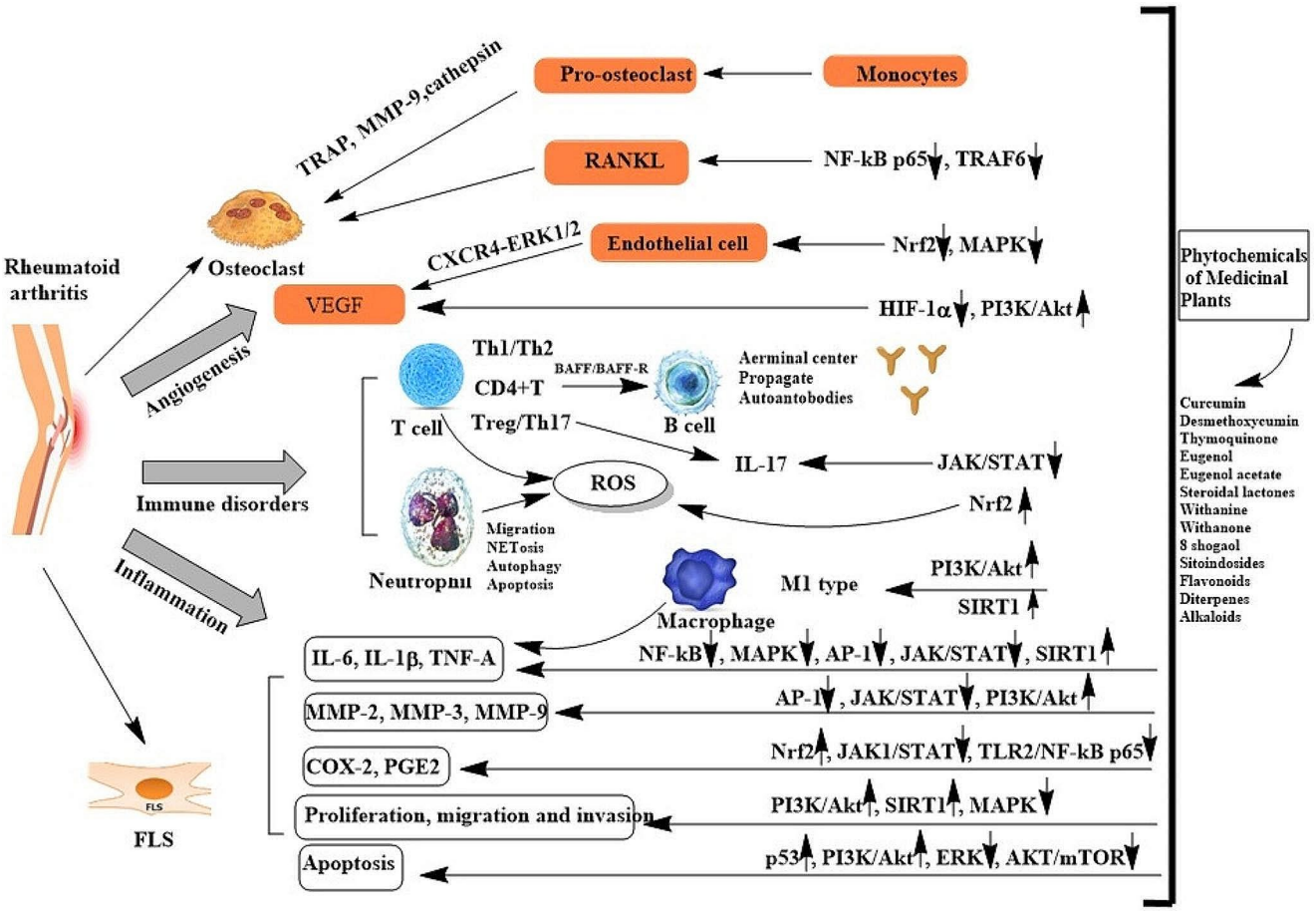

Fig. 3 Mechanisms of natural medicines (phytochemicals) against RA. ↑: increase, promote or up-regulation; ↓: decrease, down-regulation or inhibit

arthritis in the rat model [44], as shown in Fig. 4. Adipokines like leptin, adipsin, and adiponectin are suppressed by curcumin nanoparticles when applied to the mouse knee. To prevent cartilage deterioration, curcumin nanoparticles have also shown anti-inflammatory capabilities [45]. Curcumin has been discovered to be responsible for enhancing the anti-arthritic properties of other therapeutic plants, including black pepper and sarsaparilla root [46].

Nigella sativa

Nigella sativa, originally native to Southwest Asia, Southern Europe, and North Africa, is now grown in various countries, including the Middle Eastern Mediterranean region, Saudi Arabia, Pakistan, Southern Europe, Syria, India, and Turkey [47]. Due to the presence of its main phytochemical, thymoquinone, *N. sativa*'s oil and seeds have been claimed to have anti-inflammatory properties [48]. The average composition of *N. sativa* oil is 0.5-1.6% essential fatty acids, 22.7% protein, 35.6–41.6% fat (oil), and 32.2% carbohydrate. Linoleic acid makes up the majority of fixed oil in this plant (approximately 57.3%) [49].

Using an animal model of experimentally induced arthritis, the anti-RA effects of *N. sativa* and its active component TQ were examined [50]. According to a study, taking TQ orally for 21 days at a dose of 5 mg/kg per day reduced levels of inflammatory cytokines (tumor necrosis factor-alpha, interleukin-6, interferon-gamma, interleukin-1, prostaglandin E2 [PGE2]) and oxidative stress markers (myeloperoxidase, articular elastase, nitric oxide, and lipoxygenase) [49]. In a study, it was discovered that thymoquinone reduced the levels of NF-kB, IL-1, and Tumor necrosis factor-α in arthritic rats given Freund's Complete Adjuvant (FCA) [51]. Therefore, *N. sativa* can be used as a useful candidate in arthritis management. Additionally, research using human RA fibroblast-like synoviocytes in cell culture demonstrated that thymoquinone prevented the proliferation of synoviocytes induced by lipopolysaccharide (LPS), the production of 4-hydroxynonenal induced by H_2O_2 [52], and the levels of IL-1, TNF-α, metalloproteinase-13, cyclooxygenase-2, and prostaglandin E2. Thymoquinone inhibited p38, MAPK, ERK1/2, and NF-kB p65 phosphorylation caused by LPS in a time-dependent manner. Additionally, research has demonstrated that giving arthritic rats thymoquinone orally lowers the serum levels of HNE, TNF- α, and Interleukin-1 [53].

Syzygium aromaticum

Syzygium aromaticum, popularly known as clove, is a dried flower bud that is endemic to the islands of Indonesia, but has recently spread around the world [54]. Several studies have demonstrated the immunomodulatory and regenerative properties of clove oil and its constituents for the treatment of rheumatoid arthritis (RA) [55, 56]. Due to the inclusion of eugenol acetate, β-caryophyllene, and eugenol (EU) as the main components, studies have shown that clove has excellent antibacterial, analgesic, antioxidant, and anesthetic qualities [56].

Eugenol, which makes up 45–90% of clove oil, is responsible for the anti-inflammatory benefits of cloves by blocking the nuclear factor-kappa B signaling pathway and preventing the production of several cytokines [57]. Additionally, by preventing the generation of cytokines in macrophages, eugenol dimers demonstrated chemopreventive effects. Eugenol may also have anti-inflammatory effects on arthritis, making it a potential treatment against the disease [58].

Withania somnifera

W. somnifera is a xerophytic plant that nurtures abundantly in Africa, Pakistan, the Mediterranean, Sri Lanka, and India [59]. Ashwagandha, also known as *Withania somnifera*, is a plant in the Solanaceae family that is extensively used in Ayurvedic medicine to treat different conditions, such as cardiovascular disease, anxiety, arthritis, asthma, amnesia, hepatitis, and neurological illnesses [60]. *W. somnifera* found to contain steroidal lactones known as withanolides that are pharmacologically active. Alkaloids from the plant's roots known as withanine make up 38% of the total weight of all known alkaloids [60]. In the form of leaves, roots, flowers, roots, and stems, 29 common metabolites produced from the leaf and root extracts have medicinal value [61]. With a long history that dates back to the year 6,000, *W. somnifera* has been utilized medicinally. The plant's primary metabolites include withanolides, including withanolide A, withanone, and withaferin A, as well as withanosides, sitoindosides, and other alkaloids that may have therapeutic and medicinal uses [62]. *W. somnifera* has anti-arthritic qualities because it inhibits inflammatory chemicals and increases antioxidant activity [63]. Additionally, it has been noted that *W. somnifera* extract reduces the collagenolytic activity, which further inhibits collagen degradation [46]. Several clinical studies have also been conducted to determine the effectiveness of *W. somnifera* extracts in treating joint pain, and the extracts are successful in treating arthritic conditions [64].

Zingiber officinale

Ginger is a key ingredient in different alternative medicine systems and is one of the known culinary and medicinal ingredients in the world [65]. It is effective against arthritis, rheumatological diseases, muscular aches, headaches,

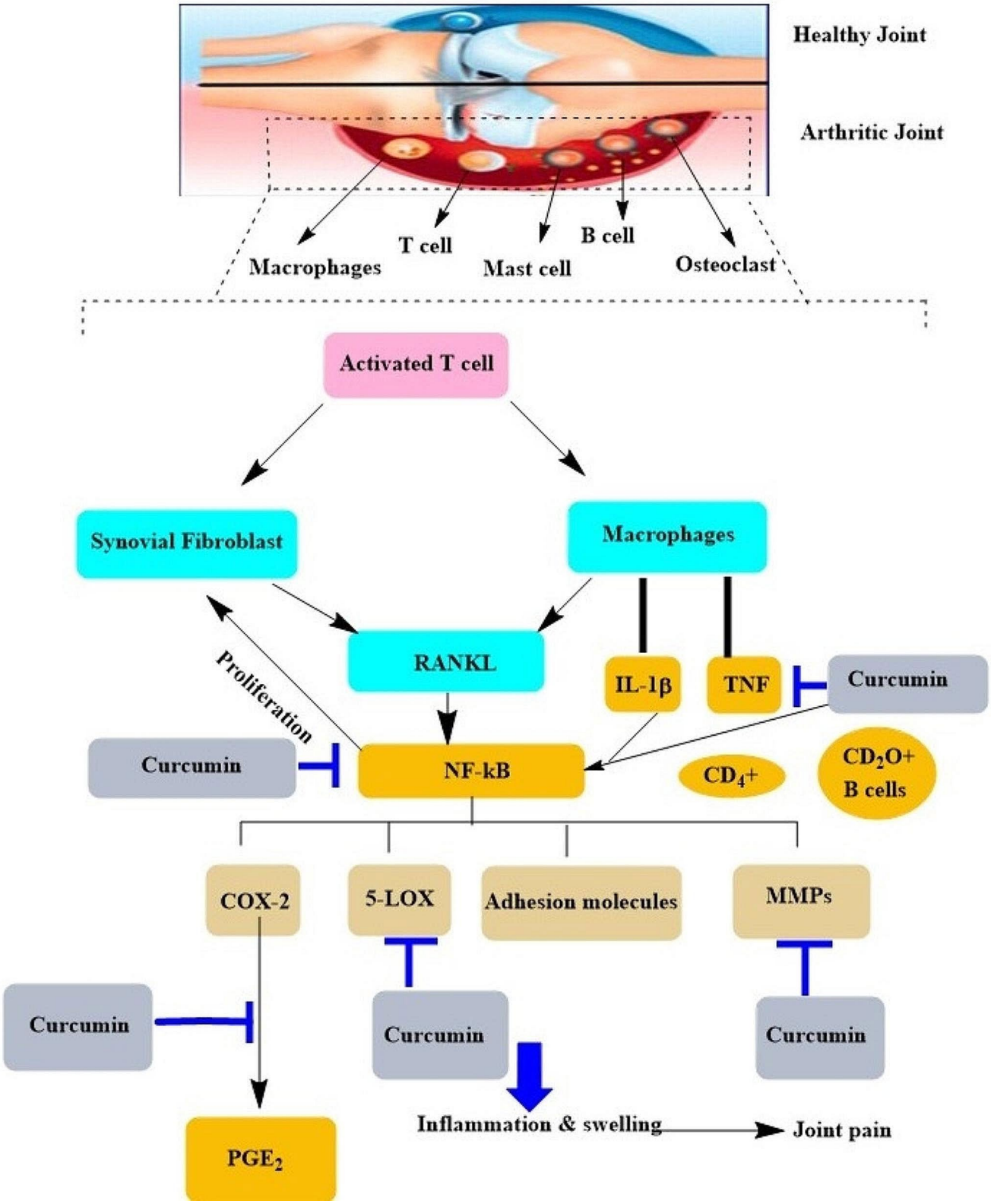

Fig. 4 Immunomodulatory effects of curcumin on dysregulated immune cells in RA

nausea, stomach distress, diarrhea, and colds. It also acts as a carminative and an antiflatulent [66]. In both preclinical and clinical investigations, ginger has received extensive attention for its anti-arthritic properties. Rats' paws and joint swelling brought on by *Mycobacterium tuberculosis* are significantly reduced by ginger oil. The ginger extract in alcohol was efficient in lowering inflammation and collagen-induced arthritis in rats [43].

By upregulating the expression of the forkhead-box-P3 (FoxP3) gene and downregulating the expression of T-bet and retinoic acid receptor-related orphan nuclear receptor gamma (RORγt) genes, ginger (rhizomes of *Zingiber officinale*) improved RA as shown in Fig. 5 [67]. FoxP3 expression promotes the growth and functionality of regulatory T (T-reg) cells, as it is a crucial transcription factor for T-reg cells [68]. TGF-β and IL-10, two immunomodulatory cytokines, are produced when T-reg cells are activated, and they also lessen inflammation [69]. It is widely believed that RORγt is a key regulator of Th17 cell differentiation and IL-17 cytokine production, both of which are critical for the onset of several autoimmune diseases, including arthritis. Immune cell transcription factor T-bet is said to control the generation of the pro-inflammatory cytokine IL-1α in dendritic cells [70]. Both of these transcription factor genes combined expression levels are declined, which may aid in lessening RA [71].

Mechanistic studies demonstrate that the therapeutic actions of ginger or its phytochemicals are mediated by scavenging free radicals [72], increasing antioxidant enzymes and antioxidant molecules, reducing the leukocyte infiltration (including macrophages /monocytes and lymphocytes) into the synovial cavity of the knee [73], inhibiting iNOS and nitric oxide anti-inflammatory activity, and by suppressing prostaglandin synthesis through inhibition of cyclooxygenase-2 and − 1 [43].

8-Shogaol had strong inhibitory effects on TNF-α, IL-6, and IL-8-mediated inflammation and migration [74]. 8-Shogaol directly and specifically reduced TAK1 activity, which in turn repressed the MAPK, Akt, and IKK signaling pathways as shown in Fig. 6. Furthermore, in the adjuvant-induced arthritic (AIA) rat model, 8-shogaol therapy decreased paw thickness and enhanced walking ability [75].

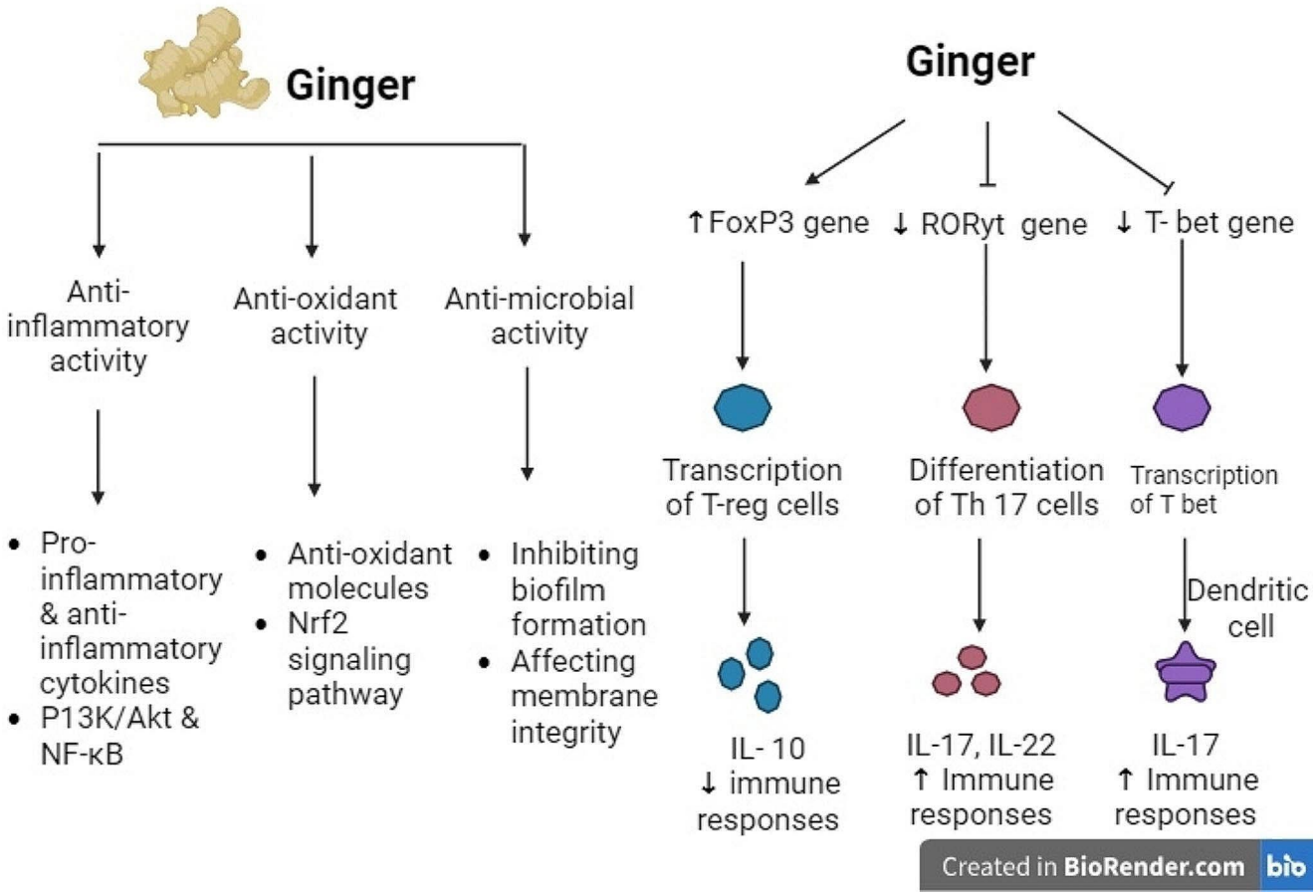

Fig. 5 Biological activities and simplified mechanisms of the immunomodulatory effects of *Zingiber officinale*. Abbreviations—T-reg cells: regulatory T-lymphocytes; Th17: helper T-lymphocyte 17; IL: interleukin; FoxP3: forkhead-box-P3; RORγt: retinoic-acid-receptor-related orphan nuclear receptor gamma

By boosting the anti-inflammatory cytokines production while lowering the production of pro-inflammatory cytokines and activating the antioxidant system, ginger has been discovered to have antiarthritic properties. *Z. officinale* also has strong anti-inflammatory and anti-rheumatic capabilities [76].

Tinospora cordifolia

Tinospora cordifolia, also known as Amruta in Ayurveda, has great therapeutic value as well as effective analgesic, anti-inflammatory, and immunomodulatory qualities [46]. The anti-inflammatory and antioxidant activity of *T. cordifolia* was examined in activated human monocytic (THP-1) cells because the traditional use of the plant has been scientifically supported using animal models for numerous disorders [77]. By interacting with endothelial cells, which later develop into macrophages in the artery lumen, the model system, which is activated by external stress factors at early stages of inflammation, plays a crucial role in generating vascular inflammation and numerous inflammatory disorders [78].

Additionally, *T. cordifolia* is said to inhibit NF-kB in THP-1 cells, demonstrating its anti-inflammatory capabilities [77]. *T. cordifolia* extract also has been shown to have anti-arthritic characteristics by reducing the release of chemokines and cytokines such as Interleukin-1, TNF-α, Interleukin-17, and Interleukin-6 in a study employing the rat adjuvant-induced arthritis model of human RA [46, 79].

Commiphora wightii

The Buseraceae plant, *Commiphora wightii*, which grows in northern India and is often referred to as Guggulu in Ayurveda, produces a fragrant resin that has been used to cure a variety of ailments, including cardiac illnesses, inflammation, high cholesterol, arthritis, and obesity [80, 81]. There are other names for it, including guggula, guggul, guggal, gugar, and Indian bdellium [82]. Guggul resin is mostly made up of volatile oil, which is rich in sesquiterpenoids and terpenoids including monoterpenoids, as well as additional terpenoids (di- and triterpenoids), steroids [83], guggultetrols, flavonoids, lignans, sugars, and amino acids [84]. Inhibiting the synthesis of inflammatory molecules like TNF-α, interleukin-1, interleukin-6, and interleukin-23 as well as iNOS and COX-2, has been shown to prevent cartilage deterioration by a lipid-rich extract isolated, guggulipid from *C. wightii* [85]. In an in vivo Freund's full adjuvant-induced arthritic rat model, guggulipid has additionally shown a strong ability to diminish the oxidative

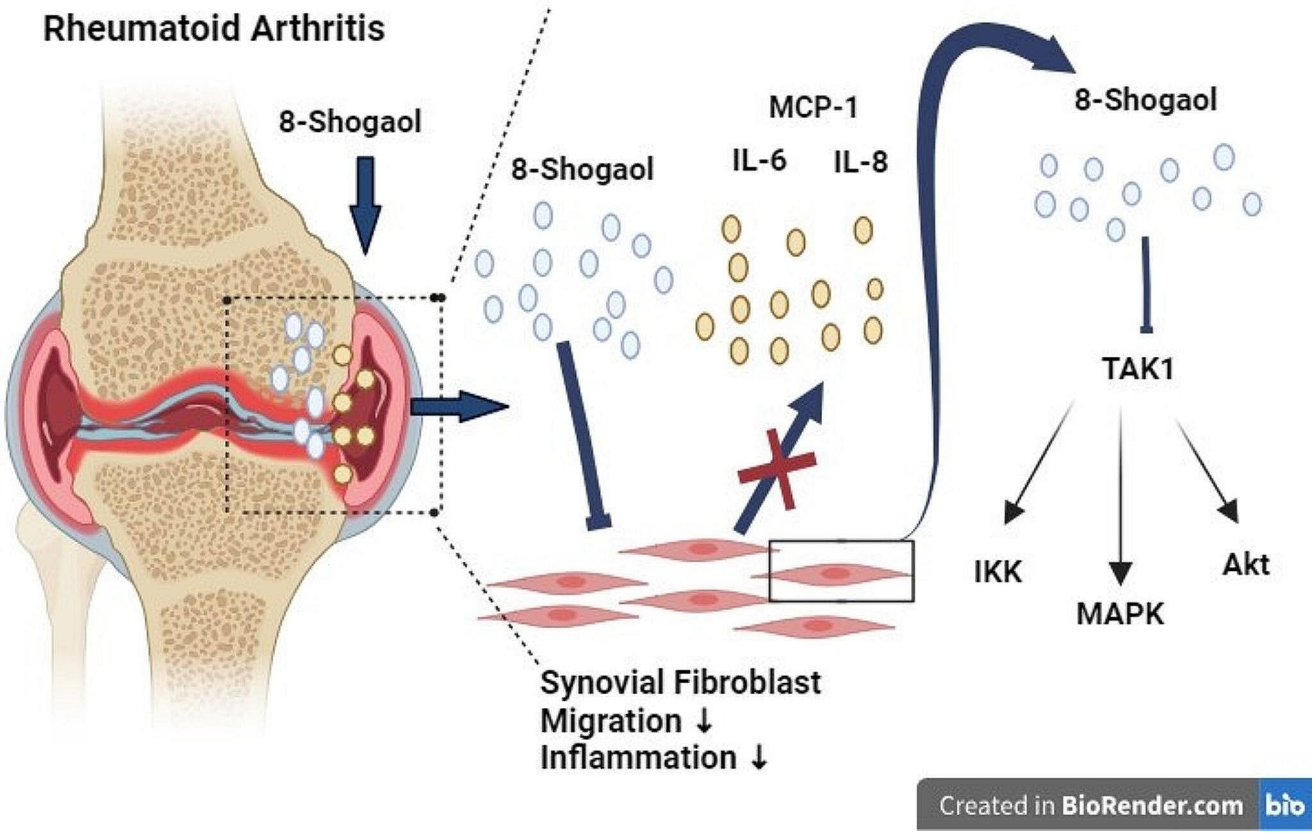

Fig. 6 Role of 8- Shogaol against Rheumatoid Arthritis by targeting TAK1 activity

stress generated during the onset of arthritic symptoms [46, 86].

Tripterygium wilfordii

Traditional Chinese herb *Tripterygium wilfordii Hook F.* (TwHF) is commonly grown in Korea, south and east of China, and Japan [87]. It has been used for a very long time in traditional Chinese medicine (TCM), frequently for rheumatoid arthritis [88]. TwHF has demonstrated a variety of pharmacological effects, including anticancer, anti-inflammatory, immuno-suppressive, anti-oxidative, and antifertility effects [89, 90]. Many preclinical studies have specifically shown cartilage-protective, immuno-suppressive, and anti-inflammatory benefits concerning its treatment for RA [91]. TwHF contains more than 500 isolated and recognized chemical components, including glycosides, sesquiterpenes, lignans, diterpenes, alkaloids, triterpenes, and flavonoids [92, 93]. Activating collaterals and blood circulation, reducing pain and swelling, and preventing rheumatism are just a few of the advantages of using TwHF, an herb that is said to be effective in arthralgia relief, according to traditional Chinese medicine (TCM) theory. A growing body of clinical research has demonstrated that TwHF-based therapy may be more successful than DMARD monotherapy at reducing the severity of RA illness [94, 95]. Following TwHF-based therapy, several patients may experience a variety of negative consequences, although these effects can be mitigated by using the proper treatment and management techniques [96]. Furthermore, Lv *et al*. recently discovered that MTX with TwHF therapy for treating RA was superior to both TwHF and MTX monotherapies [97]. As a result, more extensive clinical trials are still required to look into the safety, long-term effectiveness, and ideal dosages of using TwHF and MTX together to treat RA [98].

Boswellia serrata

The resin oleo-gum of the *Boswellia serrata* tree is one such folk remedy that has long been utilized for cosmetic, medicinal, and ceremonial purposes. The plant's oleo-gum resin is also used in traditional medicine to treat a wide range of ailments, such as inflammatory diseases like chronic pain, asthma, gastrointestinal issues, arthritis, and many other illnesses [99, 100]. Additionally, *Boswellia serrata* is mentioned throughout the Astanga Samgraha, Charaka Samhita, Astanga Hridaya, and Susruta Samhita original texts [101]. The oleo-gum resins of the tree have been described as an antiarthritic agent in the Susruta Samhita and Charaka Samhita. Additionally, it has been suggested for usage both externally and internally in several inflammatory disorders by the Unani and Ayurvedic medical systems [100].

Boswellia serrata acts to inhibit pro-inflammatory cytokines. It suppresses interferon-γ (IFN-γ), interleukin-1 β (IL-1 β), tumor necrosis factor-α (TNF-α), and increases the production of Interleukin-10 in collagen-induced arthritic rats. These cytokines have a crucial role in tissue damage during the progression of RA and chronic inflammation [81, 102]. Flavonoids, terpenoids, phenylpropanoids, and phenolic compounds were found to be the primary components in the gum resin of *B. serrata*, according to a phytochemical analysis using thin-layer chromatography [103]. *B. serrata* extract contains more than 12 distinct boswellic acids, but only AKBA (3-O-acetyl-11-keto-boswellic acid) and KBA (11-keto-boswellic acid) have attracted significant pharmacological interest [104]. *B. serrata* also contains additional elements that are crucial to its anti-inflammatory properties, including flavonoids (kaempferol, quercetin) and phenolic chemicals [105] Table 1.

Conclusion

In conclusion, this review has described a comprehensive overview that using herbal plants to cure arthritis is more effective than synthetic medications. The effects of plant extracts containing phyto-constituents such as terpenoids, flavonoids, sterols, and alkaloids that have anti-inflammatory and antioxidant action also have been assessed. As a result, herbal medicine is increasingly preferred as a complementary and alternative therapy because it has fewer or no negative effects. In vivo, in vitro, and clinical studies on RA have revealed information about the analgesic, anti-inflammatory, immune-modulatory, and antioxidant properties. To show the toxicity mechanisms and pharmacological interactions with herbal remedies, further focused investigations are required.

Limitations and future perspective

There are certain drawbacks to using these natural products, such as, low oral bioavailability, low efficacy, short half-life, and poor absorption because of rapid phytochemical metabolism. Excessive consumption of these natural products can also cause liver and renal toxicity, eye irritation, and skin irritation. To show the toxicity mechanisms and pharmacological interactions with herbal remedies, further focused investigations are required. The novel methods such as encapsulation, nano-micelles, nanoparticles, and lipid-core nano-capsules could be used to overcome these limitations. By using these methods, the efficacy, stability, and effective targeted delivery could be improved. So, these creative approaches may open the door to the development of brand-new all-natural RA drugs.

Table 1 Medicinal plants and their phytochemicals for the treatment of Arthritis

Medicinal Plant	Model	Effects	References
Zingiber officinale Roscoe	SCW method was used to induce arthritis in Female Lewis rats.	• Suppressing cytokine activity • Significantly reduction in joint swelling	[106]
Zingiber officinale Roscoe	Arthritic Lewis rats	• Significantly reduces the levels of important pro-inflammatory cytokines such as Interleukin-23, Interleukin-1, Interleukin-6, Interleukin-17, and chemokines MCP-1, TNF-α and MIP-1 (p 0.05).	[79]
Curcuma longa	Rodents	• Anti-inflammatory activity.	[107]
Curcuma longa ethanolic extract	Albino rats	• Arthritis prevention due to its anti-inflammatory properties.	[108]
Curcuma longa aqueous extract	Male albino mice	• Showed anti-inflammatory activity	[109]
Turmeric extract	Collagen-induced arthritic rats	• Reduced the deteriorating effects on the joints and bones.	[110]
Nigella sativa oil	FCA-induced arthritic rats	• Paw volume was significantly reduced when compared to the control group CFA. • Considerable anti-nociceptive activity in the oblique hind paw in comparison to the control group CFA.	[111]
Thymoquinone (TQ)	Human RA synovial fibroblasts	• Stabilizing Mcl-1 expression to induce apoptosis. • Inhibition of TNF-α-induced Interleukin-6 and Interleukin-8 production in a dose-dependent manner. • Decrease in TNF-α-induced ICAM-1, Cad-11 expression, and VCAM-1. • Inhibition of TNF-α-induced phosphorylation of JNK and p38 in a dose-dependent pattern. • TNF-α signaling is slowed down by preventing ASK1's phosphorylation and subsequent activation.	[112]
Withania somnifera	Rats	• Inflammation, pannus formation, and vascularity are all decreased by *withania somnifera*'s anti-arthritic effects.	[113]
Withania somnifera	Rats	• Attributing an anti-arthritic effect and suppressing the rheumatoid symptoms. • The inhibition of NF-kB activation and its controlled gene expression has a significant anti-inflammatory effect.	[63]
Acori graminei rhizoma	CIA model	• Lowering of serum type II collagen IgG levels and reduction of increased blood inflammation markers including Interleukin-6 and Tumor necrosis factor-α. • Both the edema of the hind limb and inflammatory cell infiltration into the synovial membrane decreased.	[114]
Ribes orientale extract	FCA-injected arthritic rats	• Reduced paw edema • Prevented body weight loss • Increase IL-10 and IL-4 levels while decreasing IL-1, TNF-α, IL-6, and NF-kB levels	[115]
Ethanolic leave extract of *S. chirayita*	Arthritic rats	• Reduces paw edema and pro-inflammatory cytokines including TNF-α and IL-1 in rats with arthritis.	[116]

Acknowledgements Not applicable.

Author contributions A. wrote and edited the manuscript and did the software work. S.A. edited and evaluated the manuscript. M.S. edited the manuscript and helped in data acquisition regarding the mechanism of action. S.Y. proofread and edited the manuscript. L.N. proofread and edited the manuscript. S.N. proofread and edited the manuscript.

Funding Funding was not available for this study.

Data availability No datasets were generated or analysed during the study.

Declarations

Ethical approval No animal was used in current study, so ethical statement is not applicable.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals per-

formed by any of the authors.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

Competing interests The authors declare no competing interests.

References

1. Grundy SM, Vega GL (2022) Statin intolerance and noncompliance: an empiric approach. Am J Med 135:318–323
2. Brennan-Olsen SL, Cook S, Leech M et al (2017) Prevalence of arthritis according to age, sex and socioeconomic status in six low and middle income countries: analysis of data from the World Health Organization study on global AGEing and adult health (SAGE) Wave 1. BMC Musculoskelet Disord 18:1–12
3. Colquhoun M, Gulati M, Farah Z, Mouyis M (2022) Clinical features of rheumatoid arthritis. Medicine 50:138–142
4. Park H (2021) Dense collagen scaffolds for bone and ligament tissue Engineering. McGill University (Canada)
5. Harth M, Nielson WR (2019) Pain and affective distress in arthritis: relationship to immunity and inflammation. Expert Rev Clin Immunol 15:541–552
6. Tateiwa D, Yoshikawa H, Kaito T (2019) Cartilage and bone destruction in arthritis: pathogenesis and treatment strategy: a literature review. Cells 8:818
7. Ahlers MJ, Lowery BD, Farber-Eger E et al (2020) Heart failure risk associated with rheumatoid arthritis–related chronic inflammation. J Am Heart Association 9, e014661
8. Gupta M (2017) Natural products in treatment of rheumatoid arthritis. Int J Green Pharm (IJGP) 11
9. Xu Y, Wu Q (2021) Prevalence trend and disparities in rheumatoid arthritis among US adults, 2005–2018. J Clin Med 10:3289
10. Karami J, Aslani S, Jamshidi A, Garshasbi M, Mahmoudi M (2019) Genetic implications in the pathogenesis of rheumatoid arthritis; an updated review. Gene 702:8–16
11. Liu X, Wang Z, Qian H et al (2022) Natural medicines of targeted rheumatoid arthritis and its action mechanism. Front Immunol 13:945129
12. Hu X-X, Wu Y-j, Zhang J, Wei W (2019) T-cells interact with B cells, dendritic cells, and fibroblast-like synoviocytes as hub-like key cells in rheumatoid arthritis. Int Immunopharmacol 70:428–434
13. Singh S, Singh TG, Mahajan K, Dhiman S (2020) Medicinal plants used against various inflammatory biomarkers for the management of rheumatoid arthritis. J Pharm Pharmacol 72:1306–1327
14. Nimesh S (2018) Herbal drug is better than allopathic drug in the treatment of rheumatoid arthritis. Int J Pharmacogn 5:539–545
15. Gautam S, Kumar R, Kumar U, Kumar S, Luthra K, Dada R (2023) Yoga maintains Th17/Treg cell homeostasis and reduces the rate of T cell aging in rheumatoid arthritis: a randomized controlled trial. Sci Rep 13:14924
16. Jeong J-W, Lee HH, Lee KW et al (2016) Mori folium inhibits interleukin-1β-induced expression of matrix metalloproteinases and inflammatory mediators by suppressing the activation of NF-κB and p38 MAPK in SW1353 human chondrocytes. Int J Mol Med 37:452–460
17. Asif Amin M, Fox DA, Ruth JH (2017) Synovial cellular and molecular markers in rheumatoid arthritis
18. Gentile P, De Angelis B, Agovino A, Orlandi F, Migner A, Di Pasquali C, Cervelli V (2016) Use of platelet rich plasma and hyaluronic acid in the treatment of complications of achilles tendon reconstruction. World J Plast Surg 5:124
19. Deng Z, Lin Z, Zhong Q et al (2021) Interleukin 1 beta-induced chloride currents are important in osteoarthritis onset: an in vitro study. Acta Biochim Biophys Sin 53:400–409
20. Buhrmann C, Brockmueller A, Mueller A-L, Shayan P, Shakibaei M (2021) Curcumin attenuates environment-derived osteoarthritis by Sox9/NF-kB signaling axis. Int J Mol Sci 22:7645
21. Pattappa G, Schewior R, Hofmeister I et al (2019) Physioxia has a beneficial effect on cartilage matrix production in interleukin-1 beta-inhibited mesenchymal stem cell chondrogenesis. Cells 8:936
22. Lefebvre V, Dvir-Ginzberg M (2017) SOX9 and the many facets of its regulation in the chondrocyte lineage. Connect Tissue Res 58:2–14
23. Elango J, Zamora-Ledezma C, Ge B et al (2022) Paradoxical duel role of collagen in rheumatoid arthritis: cause of inflammation and treatment. Bioengineering 9:321
24. Wiegertjes R, van de Loo FA, Blaney Davidson EN (2020) A roadmap to target interleukin-6 in osteoarthritis. Rheumatology 59:2681–2694
25. Wiegertjes R, Van Caam A, Van Beuningen H et al (2019) TGF-β dampens IL-6 signaling in articular chondrocytes by decreasing IL-6 receptor expression. Osteoarthr Cartil 27:1197–1207
26. Mateen S, Zafar A, Moin S, Khan AQ, Zubair S (2016) Understanding the role of cytokines in the pathogenesis of rheumatoid arthritis. Clin Chim Acta 455:161–171
27. Luan J, Hu Z, Cheng J et al (2021) Applicability and implementation of the collagen–induced arthritis mouse model, including protocols. Experimental Therapeutic Med 22:1–10
28. Rosloniec EF, Whittington K, Proslovsky A, Brand DD (2021) Collagen-induced arthritis mouse model. Curr Protocols 1, e313
29. Khan MA, Sarwar AHMG, Rahat R, Ahmed RS, Umar S (2020) Stigmasterol protects rats from collagen induced arthritis by inhibiting proinflammatory cytokines. Int Immunopharmacol 85:106642
30. He L, Luan H, He J et al (2021) Shikonin attenuates rheumatoid arthritis by targeting SOCS1/JAK/STAT signaling pathway of fibroblast like synoviocytes. Chin Med 16:1–15
31. Deane KD (2013) Can rheumatoid arthritis be prevented? Best Pract Res Clin Rheumatol 27:467–485
32. Muehleman C, Green J, Williams J, Kuettner K, Thonar E-M, Sumner D (2002) The effect of bone remodeling inhibition by zoledronic acid in an animal model of cartilage matrix damage. Osteoarthr Cartil 10:226–233
33. Grigor C, Capell H, Stirling A et al (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet 364:263–269
34. Sharma A, Goel A (2023) Pathogenesis of rheumatoid arthritis and its treatment with anti-inflammatory natural products. Mol Biol Rep 50:4687–4706
35. Choudhary M, Kumar V, Malhotra H, Singh S (2015) Medicinal plants with potential anti-arthritic activity. J Intercultural Ethnopharmacol 4:147
36. Feng Y, Zhang R, Zhao Z, He Y, Pang X, Wang D, Sun Z (2023) Efficacy and safety of electroacupuncture combined with medication for rheumatoid arthritis: A systematic review and meta-analysis. Heliyon
37. Sharma A, Khanna S, Kaur G, Singh I (2021) Medicinal plants and their components for wound healing applications. Future J Pharm Sci 7:1–13
38. Gandhi Y, Kumar R, Grewal J et al (2022) Advances in anti-inflammatory medicinal plants and phytochemicals in the management of arthritis: a comprehensive review. Food Chem Adv, 100085

39. Paschke S, Weidner AF, Paust T, Marti O, Beil M, Ben-Chetrit E (2013) Technical advance: inhibition of neutrophil chemotaxis by colchicine is modulated through viscoelastic properties of subcellular compartments. J Leukoc Biol 94:1091–1096
40. Ma Q, Jiang J-G (2016) Functional components from nature-derived drugs for the treatment of rheumatoid arthritis. Curr Drug Targets 17:1673–1686
41. Das K (2016) Turmeric (Curcuma longa) oils; in Essential oils in food preservation, flavor and safety 835–841, Elsevier
42. Baliga MS, Mane PP, Nallemgera JT, Thilakchand KR, Kalekhan F (2015) Dietary spices in the prevention of rheumatoid arthritis: past, present, and future; in Foods and Dietary supplements in the Prevention and Treatment of Disease. Elsevier. in Older Adults 41–49
43. Fuloria S, Mehta J, Chandel A et al (2022) A comprehensive review on the therapeutic potential of Curcuma longa Linn. In relation to its major active constituent curcumin. Front Pharmacol 13:820806
44. Rinkunaite I, Simoliunas E, Alksne M, Dapkute D, Bukelskiene V (2021) Anti-inflammatory effect of different curcumin preparations on adjuvant-induced arthritis in rats. BMC Complement Med Ther 21:1–12
45. Wang Y, Boulic M, Phipps R, Plagmann M, Cunningham C, Guyot G (2023) https://www.sciencedirect.com/science/article/pii/S2352710223009816? CMX_ID=&SIS_ID=&dgcid=STMJ_AUTH_SERV_PUBLISHED&utm_acid=229490816&utm_campaign=STMJ_AUTH_SERV_PUBLISHED&utm_in=DM368176&utm_medium=email&utm_source=AC_.
46. Martin BR (2020) Treatment of Psoriatic Arthritis with acupuncture, Turmeric (Curcuma longa), sarsaparilla (Smilax Officinalis) and vitamin D: a Case Report. J Chiropr Med 19:194–200
47. Thakur S, Kaurav H, Chaudhary G (2021) Nigella sativa (Kalonji): a black seed of miracle. Int J Res Rev 8:342–357
48. Sharma D, Chaubey P, Suvarna V (2021) Role of natural products in alleviation of rheumatoid arthritis—A review. J Food Biochem 45, e13673
49. Hadi V, Pahlavani N, Malekahmadi M et al (2021) Nigella sativa in controlling type 2 diabetes, cardiovascular, and rheumatoid arthritis diseases: molecular aspects. J Res Med Sciences: Official J Isfahan Univ Med Sci 26
50. Umar S, Zargan J, Umar K, Ahmad S, Katiyar CK, Khan HA (2012) Modulation of the oxidative stress and inflammatory cytokine response by thymoquinone in the collagen induced arthritis in Wistar rats. Chemico-Biol Interact 197:40–46
51. Arjumand S, Shahzad M, Shabbir A, Yousaf MZ (2019) Thymoquinone attenuates rheumatoid arthritis by downregulating TLR2, TLR4, TNF-α, IL-1, and NFκB expression levels. Biomed Pharmacother 111:958–963
52. Darakhshan S, Pour AB, Colagar AH, Sisakhtnezhad S (2015) Thymoquinone and its therapeutic potentials. Pharmacol Res 95:138–158
53. Behl T, Mehta K, Sehgal A et al (2022) Exploring the role of polyphenols in rheumatoid arthritis. Crit Rev Food Sci Nutr 62:5372–5393
54. Batiha GE-S, Beshbishy AM, Tayebwa DS, Shaheen HM, Yokoyama N, Igarashi I (2019) Inhibitory effects of Syzygium aromaticum and Camellia sinensis methanolic extracts on the growth of Babesia and Theileria parasites. Ticks tick-borne Dis 10:949–958
55. Jabbari N, Eftekhari Z, Roodbari NH, Parivar K (2020) Evaluation of Encapsulated Eugenol by Chitosan Nanoparticles on the aggressive model of rheumatoid arthritis. Int Immunopharmacol 85:106554
56. Shakeel F, Alam P, Ali A et al (2021) Investigating antiarthritic potential of nanostructured clove oil (Syzygium aromaticum) in FCA-induced arthritic rats: Pharmaceutical action and delivery strategies. Molecules 26:7327
57. Zewail MB, El-Gizawy SA, Asaad GF, Shabana ME, El-Dakroury WA (2023) Chitosan coated clove oil-based nanoemulsion: an attractive option for oral delivery of leflunomide in rheumatoid arthritis. Int J Pharm 643:123224
58. Batiha GE-S, Alkazmi LM, Wasef LG, Beshbishy AM, Nadwa EH, Rashwan EK (2020) Syzygium aromaticum L.(Myrtaceae): traditional uses, bioactive chemical constituents, pharmacological and toxicological activities. Biomolecules 10
59. Kalra R, Kaushik N (2017) Withania somnifera (Linn.) Dunal: a review of chemical and pharmacological diversity. Phytochem Rev 16:953–987
60. Saleem S, Muhammad G, Hussain MA, Altaf M, Bukhari SNA (2020) Withania somnifera L.: insights into the phytochemical profile, therapeutic potential, clinical trials, and future prospective. Iran J Basic Med Sci 23:1501
61. Yadav G, Meena M (2021) Bioprospecting of endophytes in medicinal plants of Thar Desert: an attractive resource for biopharmaceuticals. Biotechnol Rep 30, e00629
62. Bhat JA, Akther T, Najar RA, Rasool F, Hamid A (2022) Withania somnifera (L.) Dunal (Ashwagandha); current understanding and future prospect as a potential drug candidate. Front Pharmacol 13:1029123
63. Khan MA, Ahmed RS, Chandra N, Arora VK, Ali A (2019) In vivo, extract from Withania somnifera root ameliorates arthritis via regulation of key immune mediators of inflammation in experimental model of arthritis. Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Inflammatory and Anti-Allergy Agents) 18, 55–70
64. Kanjilal S, Gupta AK, Patnaik RS, Dey A (2021) Analysis of clinical trial registry of India for evidence of anti-arthritic properties of Withania somnifera (ashwagandha). Altern Ther Health Med 27:58–66
65. Badnale AB, Sarukh VS, Nikam YP, Supekar AV, Khandagale SS (2022) A review on potential medicinal herbs as health promoters. J Drug Delivery Ther 12:225–229
66. Liu X, Meng X, Su X, Ren K, Ning C, Qi X, Zhang S (2022) The mechanism of ginger and its processed products in the treatment of estradiol valerate coupled with oxytocin-induced dysmenorrhea in mice via regulating the TRP ion channel-mediated ERK 1/2/NF-κB signaling pathway. Food Funct 13:11236–11248
67. Aryaeian N, Shahram F, Mahmoudi M, Tavakoli H, Yousefi B, Arablou T, Karegar SJ (2019) The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active rheumatoid arthritis. Gene 698:179–185
68. Pereira LMS, Gomes STM, Ishak R, Vallinoto ACR (2017) Regulatory T cell and forkhead box protein 3 as modulators of immune homeostasis. Front Immunol 8:605
69. Paul AK, Jahan R, Paul A et al (2022) The role of medicinal and aromatic plants against obesity and arthritis: a review. Nutrients 14:985
70. Wang J, Fathman JW, Lugo-Villarino G, Scimone L, von Andrian U, Dorfman DM, Glimcher LH (2006) Transcription factor T-bet regulates inflammatory arthritis through its function in dendritic cells. J Clin Investig 116:414–421
71. Ecoeur F, Weiss J, Kaupmann K, Hintermann S, Orain D, Guntermann C (2019) Antagonizing retinoic acid-related-orphan receptor gamma activity blocks the T helper 17/interleukin-17 pathway leading to attenuated pro-inflammatory human keratinocyte and skin responses. Front Immunol 10:577
72. Saberi H, Keshavarzi B, Shirpoor A, Gharalari FH, Rasmi Y (2017) Rescue effects of ginger extract on dose dependent

radiation-induced histological and biochemical changes in the kidneys of male Wistar rats. Biomed Pharmacother 94:569–576
73. Moura FA, de Andrade KQ, Dos Santos JCF, Araújo ORP, Goulart MOF (2015) Antioxidant therapy for treatment of inflammatory bowel disease: does it work? Redox Biol 6:617–639
74. Al-Nahain A, Jahan R, Rahmatullah M (2014) Zingiber officinale: A potential plant against rheumatoid arthritis. Arthritis 2014
75. Jo S, Samarpita S, Lee JS et al (2022) 8-Shogaol inhibits rheumatoid arthritis through targeting TAK1. Pharmacol Res 178:106176
76. Karunakaran R, Sadanandan SP (2019) Zingiber officinale: anti-inflammatory actions and potential usage for arthritic conditions; in bioactive food as dietary interventions for arthritis and related inflammatory diseases. Elsevier, pp 233–244
77. Reddi KK, Tetali SD (2019) Dry leaf extracts of Tinospora cordifolia (Willd.) Miers attenuate oxidative stress and inflammatory condition in human monocytic (THP-1) cells. Phytomedicine 61:152831
78. Arunachalam K, Yang X, San TT (2022) Tinospora cordifolia (Willd.) Miers: Protection mechanisms and strategies against oxidative stress-related diseases. J Ethnopharmacol 283:114540
79. Sannegowda K, Venkatesha S, Moudgil K (2015) Tinospora cordifolia inhibits autoimmune arthritis by regulating key immune mediators of inflammation and bone damage. Int J ImmunoPathol Pharmacol 28:521–531
80. Ahmad MA, Mujeeb M, Akhtar M, Khushtar M, Arif M, Haque MR (2020) Guggulipid: a promising multi-purpose herbal medicinal agent. Drug Res 70:123–130
81. Kumar R, Singh S, Saksena AK, Pal R, Jaiswal R, Kumar R (2019) Effect of Boswellia serrata extract on acute inflammatory parameters and tumor necrosis factor-α in complete Freund's adjuvant-induced animal model of rheumatoid arthritis. Int J Appl Basic Med Res 9:100
82. Sarup P, Bala S, Kamboj S (2015) Pharmacology and phytochemistry of oleo-gum resin of Commiphora wightii (Guggulu). Scientifica 2015
83. Kunnumakkara AB, Banik K, Bordoloi D et al (2018) Googling the Guggul (Commiphora and Boswellia) for prevention of chronic diseases. Front Pharmacol 9:686
84. Sarup P, Pahuja S, Malik J (2022) Chemistry, biological activities, and uses of oleo-gum resin of Commiphora Wightii; in gums, resins and latexes of Plant Origin: Chemistry, Biological activities and uses. Springer, pp 447–478
85. Prasad S, Kulshreshtha A, Lall R, Gupta SC (2021) Inflammation and ROS in arthritis: management by ayurvedic medicinal plants. Food Funct 12:8227–8247
86. Sundaram MS, Neog MK, Rasool M, Kumar GS, Hemshekhar M, Kemparaju K, Girish KS (2019) Guggulipid ameliorates adjuvant-induced arthritis and liver oxidative damage by suppressing inflammatory and oxidative stress mediators. Phytomedicine 64:152924
87. Wang X, Xue M, Gu J, Fang X, Sha X (2012) Transdermal microemulsion drug delivery system for impairing male reproductive toxicity and enhancing efficacy of Tripterygium Wilfordii Hook f. Fitoterapia 83:690–698
88. Liu J, Lee J, Hernandez MAS, Mazitschek R, Ozcan U (2015) Treatment of obesity with celastrol. Cell 161:999–1011
89. Cao L, Yan M, Li H, Zhang B, Fang P (2015) Progress on mechanism of Tripterygium Wilfordii-induced liver injury and detoxification mechanism of licorice. Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China. J Chin Materia Med 40:2537–2541
90. Chang W, He W, Li P-P, Song S-S, Yuan P-F, Lu J-T, Wei W (2016) Protective effects of Celastrol on diethylnitrosamine-induced hepatocellular carcinoma in rats and its mechanisms. Eur J Pharmacol 784:173–180
91. Bao J, Dai S-M (2011) A Chinese herb Tripterygium Wilfordii Hook F in the treatment of rheumatoid arthritis: mechanism, efficacy, and safety. Rheumatol Int 31:1123–1129
92. Chen S-R, Dai Y, Zhao J, Lin L, Wang Y, Wang Y (2018) A mechanistic overview of triptolide and celastrol, natural products from Tripterygium Wilfordii Hook F. Front Pharmacol 9:104
93. Lv H, Jiang L, Zhu M et al (2019) The genus tripterygium: a phytochemistry and pharmacological review. Fitoterapia 137:104190
94. Wang H-L, Jiang Q, Feng X-H et al (2016) Tripterygium Wilfordii Hook F versus conventional synthetic disease-modifying anti-rheumatic drugs as monotherapy for rheumatoid arthritis: a systematic review and network meta-analysis. BMC Complement Altern Med 16:1–8
95. Dudics S, Langan D, Meka RR, Venkatesha SH, Berman BM, Che C-T, Moudgil KD (2018) Natural products for the treatment of autoimmune arthritis: their mechanisms of action, targeted delivery, and interplay with the host microbiome. Int J Mol Sci 19:2508
96. Zhang C, Sun P-P, Guo H-T, Liu Y, Li J, He X-J, Lu A-P (2016) Safety profiles of Tripterygium Wilfordii Hook F: a systematic review and meta-analysis. Front Pharmacol 7:402
97. Lv Q-w, Zhang W, Shi Q et al (2015) Comparison of Tripterygium Wilfordii Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomised, controlled clinical trial. Ann Rheum Dis 74:1078–1086
98. Wang X, Zu Y, Huang L et al (2017) Treatment of rheumatoid arthritis with combination of methotrexate and tripterygium wilfordii: a meta-analysis. Life Sci 171:45–50
99. Roy NK, Parama D, Banik K et al (2019) An update on pharmacological potential of boswellic acids against chronic diseases. Int J Mol Sci 20:4101
100. Khan MA, Ali R, Parveen R, Najmi AK, Ahmad S (2016) Pharmacological evidences for cytotoxic and antitumor properties of boswellic acids from Boswellia serrata. J Ethnopharmacol 191:315–323
101. MV M, PANDITA A, PALADHI AG, INAMDAR B, PANDITA D and VALLINAYAGAM S (2023) Boswellia serrata Roxb. Potent Anticancer Medicinal Plants: Secondary Metabolite Profiling, Active Ingredients, and Pharmacological Outcomes
102. Singh D, Nainwani R, Sharma T, Gautam RK (2013) In-Vitro Anti-Inflammatory and Anti-Arthritic Activity of Hydroalcoholic Extract of PongamiaPinnata (L.) Pierre Seed. International Journal of Pharma Research & Review, Dec 2013; 2 (12): 20 25
103. Ayub MA, Hanif MA, Sarfraz RA, Shahid M (2018) Biological activity of Boswellia serrata Roxb. Oleo gum resin essential oil: effects of extraction by supercritical carbon dioxide and traditional methods. Int J Food Prop 21:808–820
104. Katragunta K, Siva B, Kondepudi N, Vadaparthi PR, Rao NR, Tiwari AK, Babu KS (2019) Estimation of boswellic acids in herbal formulations containing Boswellia serrata extract and comprehensive characterization of secondary metabolites using UPLC-Q-Tof-MSe. J Pharm Anal 9:414–422
105. Gohel K, Patel K, Shah P, Hingorani L, Gandhi T (2018) Box–Behnken design-assisted optimization for simultaneous estimation of quercetin, kaempferol, and keto-β-boswellic acid by high-performance thin-layer chromatography method. JPC-Journal Planar Chromatography-Modern TLC 31:318–326
106. Funk JL, Frye JB, Oyarzo JN, Timmermann BN (2009) Comparative effects of two gingerol-containing Zingiber officinale extracts on experimental rheumatoid arthritis. J Nat Prod 72:403–407
107. Kamarudin TA, Othman F, Ramli ESM, Isa NM, Das S (2012) Protective effect of curcumin on experimentally induced arthritic rats: detailed histopathological study of the joints and white blood cell count. EXCLI J 11:226

108. Liju VB, Jeena K, Kuttan R (2011) An evaluation of antioxidant, anti-inflammatory, and antinociceptive activities of essential oil from Curcuma longa. L Indian J Pharmacol 43:526
109. Bagad AS, Joseph JA, Bhaskaran N, Agarwal A (2013) Comparative evaluation of anti-inflammatory activity of curcuminoids, turmerones, and aqueous extract of Curcuma longa. Advances in Pharmacological and Pharmaceutical Sciences 2013
110. Anna KT, Suhana M, Das S, Faizah O, Hamzaini A (2011) Anti-inflammatory effect of Curcuma longa (turmeric) on collagen-induced arthritis: an anatomico-radiological study. Clin Ter 162:201–207
111. Nasuti C, Fedeli D, Bordoni L, Piangerelli M, Servili M, Selvaggini R, Gabbianelli R (2019) Anti-inflammatory, anti-arthritic and anti-nociceptive activities of Nigella sativa oil in a rat model of arthritis. Antioxidants 8:342
112. Umar S, Hedaya O, Singh AK, Ahmed S (2015) Thymoquinone inhibits TNF-α-induced inflammation and cell adhesion in rheumatoid arthritis synovial fibroblasts by ASK1 regulation. Toxicol Appl Pharmcol 287:299–305
113. Khaled HAS, Hanna JA, Shoukry NM, Darwesh ABE, Fares NH (2022) Therapeutic potential of Withania somnifera extract on experimental model of arthritis in rats: histological study. Front Sci Res Technol 4
114. Nho J-H, Kim A, Jung H-K et al (2019) Water extract of acori graminei rhizoma attenuates features of rheumatoid arthritis in DBA/1 mice. Evidence-Based Complementary and Alternative Medicine 2019
115. Uttra AM, Shahzad M, Shabbir A, Jahan S, Bukhari IA, Assiri AM (2019) Ribes orientale: a novel therapeutic approach targeting rheumatoid arthritis with reference to pro-inflammatory cytokines, inflammatory enzymes and anti-inflammatory cytokines. J Ethnopharmacol 237:92–107
116. Mandeville A, Cock IE (2018) Terminalia chebula Retz. Fruit extracts inhibit bacterial triggers of some autoimmune diseases and potentiate the activity of tetracycline. Indian J Microbiol 58:496–506