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Chapter

Action Mechanisms of Antirheumatic Herbal Medicines

Nima Nakisa and Mahboobeh Ghasemzadeh Rahbardar

Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory and debilitating joint disorder that causes severe impairment and reduces the quality of life. The available synthetic medicines used as standard therapy for RA have numerous side effects that can compromise their therapeutic outcomes. Thus, the demand for alternative and complementary medicines is increasing. A search of English articles in PubMed, Scopus, Google Scholar, and Web of Science databases was carried out on probable mechanisms of action of herbs with the antirheumatic property. Herbal medicines stated in folk medicine face acceptance concerns by the medical community because of the lack of scientific documents regarding their physio-pharmacological mechanisms. This chapter aims to review the possible antirheumatic effects of various herbs, including *Rosmarinus officinalis* L., *Curcuma longa*, and *Crocus sativus*, their related mechanisms, and preclinical applications, in order to recall the therapeutic properties of herbal medicine. However, more clinical trials are required to confirm the safety and efficacy of these antirheumatic herbal medicines.

Keywords: rheumatoid arthritis, antirheumatic, herbal medicine, folk medicine, complementary drugs, physio-pharmacological effects

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder that can strike men and women at any age [1]. About 1% of the world's population has been affected by RA, which has resulted in progressive articular damage, permanent impairment, and even reduced life expectancy [2]. Genetic and environmental factors have important roles in the aetiopathogenesis of RA [3]. The pathophysiology of RA is complex and mainly focuses on autoimmune response and inflammation [4]. The reactive oxygen species (ROS) damage proteins such as collagen and denature immunoglobulins that both might become autoantigens in RA [5]. Autoantibodies against immunoglobulin G (IgG) (also called rheumatoid factors (RFs)) and autoantibodies against citrullinated peptides (ACPAs) are two types of autoantibodies that can cause complement activation in RA patients [6, 7]. It was suggested that increased circulating ACPAs can promote bone loss by activating macrophages, producing B cells, organizing immune complexes or binding membrane citrullinated vimentin [8–11] which consequently ease the shift from autoimmunity to inflammation. Inflammation of the synovial membrane in RA is made up of both innate and adaptive immune cells [12]. The majority of immune responses are regulated by cytokines and chemokines including interleukin-6 (IL-6) and

tumor necrosis factor (TNF) which can induct or intensify the inflammatory response of the synovial compartment [13].

Disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are currently available drugs for RA [14]. Antirheumatic medications that are currently available for RA treatment target the inflammation and tissue swelling resulting from the disease. However, the majority of patients still experience extreme pain and physical impairment. These drugs are ineffective in preventing cartilage degradation and joint damage [15]. It was also reported that taking two or more biologic DMARDs at the same time, or a biologic DMARD with a nonbiologic DMARD, increases the risk of severe infections or cancer [16]. Other investigations have also illustrated the cardiovascular [17] and ocular [18] adverse effects of antirheumatic drugs. Therefore, the development of safe, fast-acting antirheumatic medicines is required.

Complementary and alternative medicine methods are now thought to provide adjuvant therapies to improve the chances of full remission of RA [19, 20]. Several herbal medicines have displayed pre-clinical and clinical antirheumatic properties including *Curcuma longa* L., *Rosmarinus officinalis* L., and *Crocus sativus* through their antioxidant, anti-inflammatory, anti-proliferative, and antinociceptive properties (**Figure 1**).

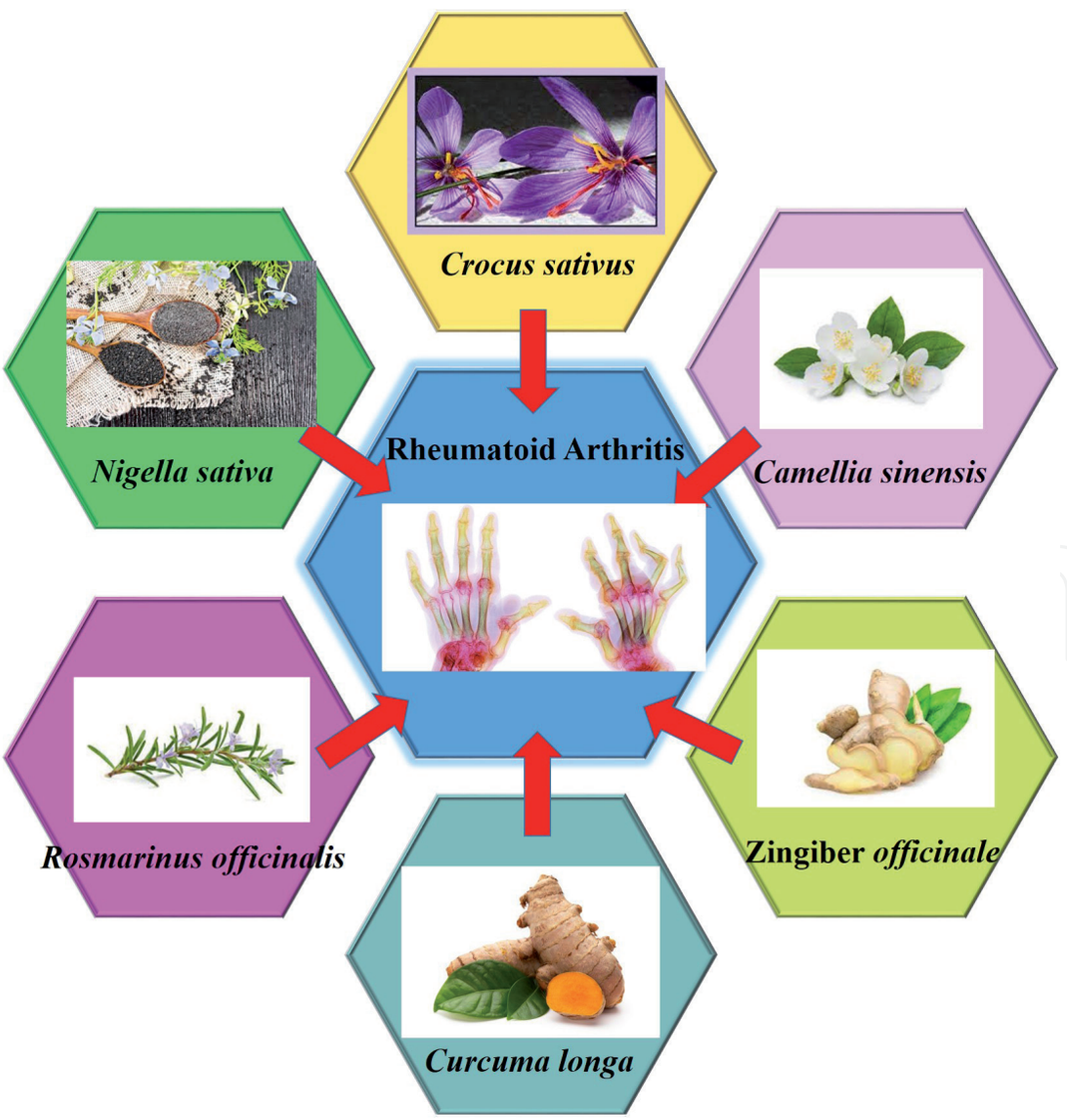


Figure 1.
Some herbal medicines with antirheumatic property.

Thus, searching for herbal medicines with antirheumatic properties could be an advantageous method to find effective antirheumatic medicines with fewer side effects. The detailed information about medicinal herbs and their physio-pharmacological mechanisms of action is summarized in this chapter.

2. Methods

The present chapter mainly emphasizes the published original articles implicating the therapeutic and beneficial effects of herbs on rheumatoid arthritis. The data (Google Scholar, PubMed, and Scopus) search has been carried out by searching related keywords, including "rheumatoid arthritis", "rosemary", "*Rosmarinus officinalis* L.", "turmeric", "*Curcuma longa* L.", "*Crocus sativus* L.", "saffron", "*Zingiber officinale*", "ginger", "*Nigella sativa*", "black seed", "black cumin", "*Camellia sinensis*", and "green tea". No time limitation was considered.

2.1 Herbal antirheumatic medicines

In folk medicine, numerous plants have been used because of their antirheumatic properties. Researchers are currently focusing on evaluating and characterization of different plants and their components to treat RA. The aim of this section of the chapter is to review the mechanism of action of a number of medicinal plants that have antirheumatic properties.

2.2 *Rosmarinus officinalis* L. (rosemary)

A former study indicated that administration of water-soluble compounds of rosemary reduced oxidative stress (by enhancing the glutathione (GSH) level and the GSH/glutathione disulfide (GSSG) ratio) and inflammation (paw edema, number of leukocytes in the femorotibial joint cavities, secondary lesions score, adrenal glands, inguinal lymph nodes, and popliteus lymph nodes weights) in rats with adjuvant-induced arthritis [21]. Carnosic acid, a major phenolic compound isolated from rosemary (5 mg/kg, 2 weeks, i.p.), administration to collagen-induced arthritis rats inhibited inflammation response and joint destruction by decreasing the amounts of TNF-α, IL-1β, IL-6, IL-8, IL-17, matrix metalloproteinase-3 (MMP-3), and receptor activator of nuclear factor kappa-B ligand (RANKL) [22] (**Table 1**). Moreover, it was observed that a methyl ester derivative of rosmarinic acid, a constituent of rosemary (50 mg/kg/day, 15 days, i.p.), has a potent anti-arthritic property in collagen-induced arthritis mice via its anti-inflammatory and immunosuppressive effects [34].

Another study has reported that rosmarinic acid triggers apoptosis via mitochondrial pathway in activated T cells taken from rheumatoid arthritis patients [35].

2.3 *Curcuma longa* L. (turmeric)

A clinical trial was carried out on 45 patients with RA to investigate the antirheumatic effect of curcumin at the dose of 500 mg for 8 weeks. Curcumin improved disease activity and the American college of rheumatology scores [36]. Another clinical trial reported that curcumin in a turmeric matrix (250 mg, twice daily, 90 days) was an advantageous agent in managing RA by its analgesic and anti-inflammatory properties. Curcumin improved erythrocyte sedimentation rate, C-reactive protein, visual analog scale, rheumatoid factor, and American College of Rheumatology responses in comparison with the control group [37]. It was also seen that administration of CuroWhite™, a novel hydrogenated curcuminoid

Herbal medicine	Antirheumatic Mechanism(s)	Reference
Rosmarinus officinalis L.	↑ GSH level	[21]
	↑ GSH/GSSG ratio	
	↓ Number of leukocytes in the femorotibial joint cavities	
	↓ TNF-α, IL-1β, IL-6, IL-8, IL-17, MMP-3, RANKL	[22]
	↑ Apoptosis	[23]
Curcuma longa L.	↓ Erythrocyte sedimentation rate	[24]
	↓ C-reactive protein	[25, 26]
	↓ PGE2, COX-2, TNF-α, and IL-1	
	↓ Bcl-2	
	↑ Bax, caspase 3, 9	[27]
	↓ MAPK/RANK/c-Fos/NFATC1	
Crocus sativus L.	↓ Erythrocyte sedimentation rate	[28]
	↓ C-reactive protein	
	↓ TNF-α, IFNγ	
	↓ MDA	[29]
	↓ Lipid peroxides	
	↑ Catalase and glutathione peroxidase	[30–33]
	↓ IL-1β, IL-6, IL-17, IL-8, NF-κB	
	↑ SOD, GR	

Bax: BCL2-associated X; Bcl-2: B-cell lymphoma-2; COX: cyclooxygenase; GSH: glutathione; GR: glutathione reductase; GSSG: glutathione disulfide; interferon gamma (IFNγ), IL: interleukin; MAPK: mitogen-activated protein kinase; MDA: malondialdehyde, MMP: matrix metalloproteinase; NFATC1: Nuclear Factor of Activated T Cells 1; NF-κB: nuclear factor kappa B; PGE2: Prostaglandin E2; RANKL: receptor activator of nuclear factor kappa-B ligand, SOD: superoxide dismutase; TNF: tumor necrosis factor.

Table 1.
Antirheumatic mechanisms of action of R. officinalis *L.,* Curcuma longa *L., and* Crocus sativus *L.*

formulation, at the dose of 250 mg and 500 mg for 3 months ameliorated RA by its anti-inflammatory and antinociceptive effects which was confirmed by improving erythrocyte sedimentation rate, rheumatoid factor, visual analog scale, and C-reactive protein [25]. A recent clinical study reported that administration of curcumin (200–1000 mg) to patients with RA decreased pain, fatigue, stiffness, and swelling [26]. The results of a clinical trial indicated that the prescription of BioSOLVE Curcumin™ (250 mg, 12 weeks) to patients with RA improved the American college of rheumatology-20, Western Ontario and McMaster universities osteoarthritis index and visual analogue scale score [28].

A turmeric extract devoid of essential oils was given to Wistar female rats in an animal model of streptococcal cell wall-induced RA. Injections of an extract containing 4 mg/kg/day total curcuminoids intraperitoneally for four days prior to arthritis induction significantly reduced joint inflammation in both the acute (75%) and chronic (68%) phases [38]. A previous investigation stated that the administration of *C. longa* extract (30, 60, and 110 mg/ml/kg, 4 weeks) prevented degenerative alterations in the joints and bones of collagen-induced arthritic rats [30]. It was also observed that turmeric (200 mg/kg, 28 days, p.o.) significantly reduced the incidence and severity of arthritis by increasing the production of anti-inflammatory agents and decreasing the amount of pro-inflammatory cytokines, as well as stimulating the anti-oxidant defense system [31]. Furthermore, turmeric

(containing 60% v/v alcohol) mother tinctures decreased hind paw swelling in carrageenan-treated rats [32].

The findings of an *in vitro* study indicated that curcumin inhibited the production of prostaglandin E2 (PGE2) and induced apoptosis in synovial fibroblasts of patients with RA by reducing the level of B-cell lymphoma-2 (Bcl-2), an anti-apoptotic protein, upregulated the amount of BCL2-associated X (Bax), a pro-apoptotic protein, and activated caspase-3 and caspase-9. Besides, curcumin attenuated the cyclooxygenase (COX)-2 mRNA expression level [23]. The findings of another research confirmed that curcumin could inhibit the osteoclastogenic potential of peripheral blood mononuclear cells from patients with RA by suppressing the mitogen-activated protein kinase/Receptor activator of nuclear factor-kappa B/c-Fos/Nuclear Factor of Activated T Cells 1 (MAPK/RANK/c-Fos/NFATC1) signaling pathways, and it was suggested that curcumin might be an effective therapeutic agent for treating bone deterioration in inflammatory diseases including RA [24]. In another investigation, human fibroblast-like synoviocytes isolated from RA patients were treated with the IC_{50} of the curcumin. Curcumin downregulated the expression of the inflammatory response gene. Moreover, the authors suggested that prescribing curcumin along with the usual therapies could increase the quality of life in RA patients [39].

The data of an *in silico* study disclosed that herbal compounds present in turmeric have strong inhibitory properties against the pro-inflammatory cytokines including TNF-α and IL-1. It was also proposed that turmeric has therapeutic potentials to be used for treating RA [40].

2.4 *Crocus sativus* L. (saffron)

A clinical trial was carried on 66 women with RA to assess the effect of saffron (100 mg/day, 12 weeks) supplementation on their metabolic profiles and clinical outcomes. According to the obtained data, saffron considerably reduced the number of swollen and tender joints, pain intensity, and disease activity score compared to baseline values. Moreover, erythrocyte sedimentation rate was significantly improved and high-sensitivity C-reactive protein, TNF-α, interferon-gamma (IFNγ), and MDA levels reduced [41].

In an *in vivo* study, the efficiency of saffron was assessed on adjuvant-induced arthritic mice. As the results showed the daily administration of the saffron extract (25, 50, and 100 mg/kg, 47 days, p.o.) decreased the amount of lipid peroxides level and increased the activity of catalase and glutathione peroxidase [42]. The effect of saffron ethanolic extract (25–600 mg, 12 days, every other day, i.p.) was studied in an adjuvant-induced arthritis rat model. The results revealed that saffron ethanolic extract chiefly at the higher concentrations meaningfully attenuated tibiotarsal joint and paw diameters in comparison to the control group. It has also been suggested that saffron ethanolic extract could be potentially used as an anti-arthritic agent in managing inflammation in RA [43]. An investigation examined the effect of saffron extract (50, 100 mg/kg, 47 days, p.o.) on adjuvant-induced arthritis in mice. It was observed that saffron could remarkably reduce TNF-α and IL-1β levels. It also increased superoxide dismutase (SOD) and glutathione reductase (GR) activity [44]. Another *in vivo* study was planned to determine the effect of crocin, a carotenoid constituent of saffron, on the rat RA model. It was seen that intradermal prescription of crocin (6.25, 12.5, and 25 mg/kg, 28 days) pointedly alleviated the paw swelling, decreased arthritis score, the thymus index, the inducible nitric oxide synthase (iNOS) production, and the serum amount of TNF-α, IL-1β, and IL-6 [27]. Moreover, it was reported that crocin (40 mg/kg, 36 days, p.o.) shows therapeutic potential for RA, by mitigating the symptoms and preventing the expression of

pro-inflammatory factors including TNF-α, IL-17, IL-6, and IL-8 in ankle tissues and serum of collagen-induced arthritic rats [29]. It was also illustrated that crocin treatment (50 mg/kg, a week, i.p.) significantly decreased the amounts of TNF-α, IL-1β, and IL-6 in collagen-induced arthritic mice through blocking nuclear factor kappa B (NF-κB) signal activation by its interaction with IκB kinase (IKK) [33] (**Table 1**).

2.5 *Zingiber officinale* (ginger)

A former clinical trial was carried out on 6 patients with RA who took ginger powder (0.5–1 g/day, 3 months). It was found that all six patients reported pain relief, improved joint mobility, decreased swelling, and morning stiffness after three months of continuous ginger intake. There were no side effects recorded by any of the participants, and they all seemed to be happier and more engaged in their daily lives [45]. Another study investigated the effect of ginger on 56 RA patients. The findings revealed that after taking ginger (50 g/day raw/fresh, 3 months-2.5 years) more than three-quarters of participants reported pain and swelling relief to varying degrees. Also, all the subjects with muscular discomfort experienced pain relief. The authors suggested that at least one of the mechanisms by which ginger exerts its beneficial effects is thought to be linked to inhibition of prostaglandin and leukotriene biosynthesis, implying that it acts as a dual eicosanoid biosynthesis inhibitor [46]. The results of another study demonstrated that ginger powder (1500 mg, 12 weeks) administration ameliorated RA by reducing disease manifestations through controlling immunity factors, for instance enhancing the gene expression of forkhead box P3 (FoxP3), as well as attenuating RAR-related orphan receptor gamma (RORγt), and T-bet genes expression [47].

Prescription of *Z. officinale* (> 50 mg/kg/day, 26 days, i.p.) amended the disease incidence, clinical scores, cartilage destruction, swelling and temperature of the joint in rat collagen-induced arthritis. It also reduced serum levels of IL-1β, IL-2, IL-6, TNF-α, and anti-collagen type II (CII) antibodies [48]. The anti-inflammatory property of the essential oil of ginger was assessed in an experimental model of RA in female rats and it was observed that ginger essential oil (28 mg/kg, 28 days, i.p.) ameliorated chronic joint inflammation. These findings indicate that the anti-inflammatory properties of ginger are due to a combination of secondary metabolites, pungent-tasting gingerols, and aromatic essential oils, rather than only the phenolic compounds that have been studied previously [49]. A recent document explained that oral administration of zingerone, an active constituent of ginger (25 mg/kg, 3 weeks), to adjuvant-induced RA rats considerably decreased the amounts of NF-κB, transforming growth factor-beta (TGF-β), TNF-α, IL-1β, IL-6, and high-sensitivity C-reactive protein (hs-CRP), and significantly enhanced IL-10 levels. Moreover, zingerone restored the amounts of antioxidant enzymes [50]. Cedrol, a ginger active component, has been shown to improves RA by decreasing inflammation and preventing Janus kinase 3 (JAK3) phosphorylation [51].

Ginger extract was found to be an advantageous anti-inflammatory agent in an *in vitro* model on cultured fibroblast-like synoviocytes from RA patients by inhibiting the production of cytokines [52].

2.6 *Nigella sativa* (black seed, black cumin)

The efficiency of *N. sativa* oil was studied in the management of RA. The subjects of the treatment group took *N. sativa* oil capsules (500 mg, twice a day, 1 month). The results disclosed that the disease activity score, the number of swollen joints, and the duration of morning stiffness remarkably reduced compared with the

placebo group [53]. Assessing the effects of *N. sativa* oil extract (500 mg, twice a day, 8 weeks) on oxidative stress status and inflammatory cytokine response in patients with RA indicated that the serum amount of IL-10 augmented in the *N. sativa* group, besides serum malondialdehyde (MDA) and nitric oxide (NO) levels decreased compared with the baseline [54]. Another clinical trial reported that administration of *N. sativa* oil (1 g/day, in two divided doses, 2 months) to 43 female patients with mild to moderate RA led to a significant decrease of the serum hs-CRP amount and the number of swollen joints. A moderately similar T helper cells ($CD4^+$ T cell) percentage was detected in the *N. sativa* oil and placebo groups. *N. sativa* also decreased CD8+, and amplified CD4+CD25+ T cell percentage and the CD4+/CD8+ ratio in comparison with the baseline and placebo group [55] (**Table 2**).

Evaluating the effects of thymoquinone, the volatile oil of black cumin (2.5, 5 mg/kg, 14 days, p.o.), on RA model in rats disclosed that signs of inflammation on the claw and the amounts of TNF-α, as well as IL-1β decreased in treatment groups

Herbal medicine	Antirheumatic Mechanism(s)	Reference
Zingiber officinale	↓ Prostaglandin and leukotriene	[47]
	↑ FoxP3	
	↓ RORγt, and T-bet	[48, 50]
	↓ IL-iβ, IL-2, IL-6, TNF-α, NF-κB, TGF-β, hs-CRP, and anti-CII antibodies	
	↑ IL-10	[51]
	↓ JAK3 phosphorylation	
Nigella sativa	↑ IL-10	[54]
	↓ MDA	
	↓ NO	
	↓ hs-CRP	[55]
	↓ CD8+	
	↑ CD4+CD25+ T cell, CD4+/CD8+ ratio	[56]
	↓ TNF-α, IL-iβ	[57]
	↓ PGE2, TNF-a, IL-ib, IL-6, IFN-c, TNF-α-induced phospho-p38 and phospho-JNK	[58]
	↓ MPO, elastase activity, lipid peroxidation, articular nitrite content	
	↑ GSH and SOD	
	↓ NFκB, TLR2, and TLR4	[59]
Camellia sinensis	↓ Oxidative stress	[60]
	↓ Blood leukocytosis and erythrocyte sedimentation rate	[61]
	↓ Free radical levels	[62]
	↓ IL-iβ, IL-6, IL-8, and COX-2	[63]

CD4+ T cell: T helper cells, CII: collagen type II, COX: cyclooxygenase; FoxP3: forkhead box P3; GSH: glutathione; hs-CRP: high-sensitivity C-reactive protein; IFN-c: Interferon-c; IL: interleukinJAK3: Janus kinase 3; JNK: c-Jun N-terminal kinases, MDA: malondialdehyde, MPO: myeloperoxidase; NF-κB: nuclear factor kappa B; NO: nitric oxide, PGE2: Prostaglandin E2; RORγt: RAR-related orphan receptor gamma; SOD: superoxide dismutase; TGF-β: transforming growth factor-beta, TLR: toll like receptor; TNF: tumor necrosis factor.

Table 2.
Antirheumatic mechanisms of action of Zingiber officinale, Nigella sativa, *and* Camellia sinensis.

[56]. Thymoquinone (5 mg/kg, 21 days, p.o.) treatment in the collagen-induced arthritis in Wistar rats could considerably reduce the amounts of pro-inflammatory mediators including PGE2, TNF-a, IL-1b, IL-6, Interferon-c (IFN-c), and increased IL-10 level. Thymoquinone also decreased arthritis scoring and improved bone histology [57]. Administration of the aqueous methanolic extract of black seed (400, 500 mg/kg, 20 days, p.o.) to arthritic rats decreased myeloperoxidase (MPO), elastase activity, lipid peroxidation, articular nitrite content, and increased GSH and SOD amounts [64]. In another rat model of RA, *N. sativa* oil (0.91, 1.82 mL/kg (798, 1596 mg/kg, respectively), 25 days, p.o.) was administered to animals. *N. sativa* oil exhibited anti-inflammatory, anti-nociceptive, and anti-arthritic properties that were significant in comparison with the untreated arthritic rats [59]. The results of an *in vivo* study demonstrated that thymoquinone (10 mg/kg, 28 days, i.p.) administration arthritic rats attenuated the macroscopic arthritic score, pannus formation, synovial inflammation, bone erosion and CRP amount. Moreover, mRNA levels of IL-1, TNF-α, NFκB, TLR2, and TLR4 were reduced [60].

An *in vitro* study explained that thymoquinone inhibited TNF-α-induced phospho-p38 and phospho-c-Jun N-terminal kinases (JNK) expression in RA synovial fibroblast [57].

2.7 *Camellia sinensis* (green tea)

Evaluating the therapeutic effects of green tea (0.5, 1.0 g/kg, 24 days, p.o.) on articular/extra-articular difficulties in rat adjuvant-induced arthritis revealed that the arthritis severity and complications besides oxidative stress ratio in synovial fluid were significantly reduced [61]. In another *in vivo* study, adjuvant-induced arthritic rats received green tea aqueous extracts (0.5 and 1.0 g/kg, p.o.) for 28 or 14 consecutive days starting from day 0 or 14 of arthritis induction, respectively). It was observed that the high dose of green tea amended synovial joint inflammation, reduced blood leukocytosis and erythrocyte sedimentation rate, and changes in weight/cellularity of lymphoid organs. It also decreased the systemic production of pro-inflammatory cytokines and the expression of chemokine receptor-5 in synovial tissues [65]. Aqua-alcoholic extract of green tea (50, 100, 200, 400 mg/kg, 14 days, p.o.) was prescribed to collagen-induced arthritic rats. The findings showed that green tea was useful in reducing the ratio of oxidative stress by controlling the amounts of antioxidants, decreasing free radical levels, and restoring normal hematopoietic cascade [58]. The therapeutic potential of green tea was evaluated in an experimental model of RA in Lewis rats. The data showed that green tea reduced paw edema, bone erosion, and inflammatory responses in joints of treated rats. It also reduced telomerase activity in comparison with the control group [62].

In an *in vitro* study, crude aqueous *C. sinensis* (50, 100, 200, 400 μg/ml) infusion and decoction revealed anti-arthritic properties in protein denaturation and membrane stability methods [66]. It was also found that catechins derived from *C. sinensis* (epigallocatechin-3-gallate, epigallocatechin, and epicatechin) inhibit the IL-1β signaling pathway and consequently decrease the amounts of pro-inflammatory mediators such as IL-6 and IL-8, as well as COX-2 in primary human RA synovial fibroblasts [63] (**Table 2**).

3. Conclusion

Herbs are spread in different geographical and ecological throughout the world. Since the olden days several traditional herbs have been utilized for treating plenty of ailments. The number of medicinal plants that have antirheumatic properties is

comparable to potent synthetic antidepressants. The antirheumatic effects of plants have been linked to their antioxidant, anti-inflammatory, analgesic properties. Furthermore, polyherbal formulations might be more effective due to their possible additive and/or synergistic effects and could be employed for ameliorating mild to moderate RA. As a result, it is possible to conclude that medicinal plants are at the center of nature and that more research is required to determine their therapeutic value.

Abbreviations

ACPAs	autoantibodies against citrullinated peptides
Bax	BCL2-associated X
Bcl-2	B-cell lymphoma-2
$CD4^+$ T cell	T helper cells
CII	collagen type II
COX	cyclooxygenase
DMARDs	disease-modifying anti-rheumatic drugs
FoxP3	forkhead box P3
GSH	glutathione
GR	glutathione reductase
GSSG	glutathione disulfide
hs-CRP	high-sensitivity C-reactive protein
IFN-c	Interferon-c
IgG	immunoglobulin G
IFNγ	interferon gamma
IKK	IκB kinase
IL	interleukin
iNOS	inducible nitric oxide synthase
JAK3	Janus kinase 3
JNK	c-Jun N-terminal kinases
MAPK	mitogen-activated protein kinase
MDA	malondialdehyde
MMP	matrix metalloproteinase
MPO	myeloperoxidase
NFATC1	Nuclear Factor of Activated T Cells 1
NF-κB	nuclear factor kappa B
NO	nitric oxide
NSAIDs	anti-inflammatory drugs
PGE2	Prostaglandin E2
RA	rheumatoid arthritis
RANK	Receptor activator of nuclear factor kappa B
RANKL	receptor activator of nuclear factor kappa-B ligand
RFs	rheumatoid factors
RORγt	RAR-related orphan receptor gamma
ROS	reactive oxygen species
SOD	superoxide dismutase
TGF-β	transforming growth factor-beta
TLR	toll like receptor
TNF	tumor necrosis factor

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update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the rheumatic diseases. 2017;76(6):1102-7.

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