Review

Phytotherapy Targeting Rheumatoid Arthritis: A Clinically Based Approach

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Abstract: Rheumatoid arthritis is a chronic autoimmune-inflammatory disease characterized by joint destruction and physical disability. The present treatment options in rheumatoid arthritis include nonsteroidal anti-inflammatory drugs, glucocorticoids, and synthetic and biological disease-modifying antirheumatic drugs. However, all these classes of medications have disadvantages associated with severe adverse reactions, patients' low adherence to treatment, and numerous drug interactions. These drawbacks emphasize the need to identify novel anti-inflammatory agents to replace or support standard therapy and improve treatment compliance. This mini-review focuses on herbal preparations whose efficacy was evaluated in clinical trials. Extracts of various plant species (*Tripterygium wilfordii* Hook F, *Paeonia lactiflora* Pallas, *Olea europea* L., *Silybum marianum* (L.) Gaertn., *Hippophaë rhamnoides* L., *Punica granatum* L., *Vaccinium macrocarpon* Aiton) and powdered plant parts (*Allium sativum* L., *Rosa canina* L.) significantly improved the clinical parameters, disease activity indices, and biochemical markers in rheumatoid arthritis patients when they were administered as supportive therapy alongside the standard medication or, more rarely, as monotherapy. The bioactive compounds have been only partially identified and further research is required to fully elucidate the phytochemical profile of these herbal preparations. Although the clinical studies performed up to now support the benefits of herbal supplementation in rheumatoid arthritis, there is a strong need for more human trials to validate the efficacy and safety of herbal preparations.

Keywords: rheumatoid arthritis; herbal preparations; disease activity indices; ACR response; EULAR response

1. Introduction

Rheumatoid arthritis (RA) is a complex, systemic, autoimmune, and inflammatory condition characterized by progressive multiple joint destruction and deformity [1]. RA is also defined by numerous extra-articular manifestations such as rheumatoid nodules, pleuro-pulmonary involvement, renal impairment, vasculitis, and accelerated atherosclerosis. Patients experience morning stiffness, fatigue, functional disability, and reduced quality of life [2–4]. The treatment of RA has evolved remarkably in recent decades, with the therapeutic arsenal now including nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and synthetic and biological disease-modifying antirheumatic drugs (DMARDs). The systemic adverse effects caused by the chronic use of NSAIDs (gastric, renal, hepatic, cardiac, and hematologic side effects) [5–11], glucocorticoids (increased risk of infections, osteoporosis, myopathy, diabetes mellitus, peptic ulcer, hypertension, increased cardiovascular risk, obesity, Cushing syndrome, cataracts, glaucoma, psychosis, depression, insomnia) [12–15], and conventional synthetic DMARDs (hepatic and pulmonary fibrosis, leukopenia, anemia, thrombocytopenia, increased risk of infections, lymphomas, teratogenic effects) [16–18], as well as the numerous drug interactions and patients' low adherence to the prescribed treatments, call for the discovery of effective and less toxic anti-inflammatory agents to replace/support standard therapy and improve treatment compliance [19–21]. In recent years, there has been an increased interest from both patients and physicians in herbal preparations. The benefits of herbal preparations in patients with RA were confirmed in numerous clinical studies. Most of them were randomized trials evaluating the benefits of herbal supplementation in RA patients undergoing various treatments compared to control or placebo [22–25]. The clinical assessment was mainly based on a set of indicators established by the American College of Rheumatology (ACR) and validated by the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT): tender and swollen joint count in 68 and 66 joints, respectively/28 joints (TJC68, SJC66, TJC28,

SJC28), morning stiffness (in min.), patient's and physician's global assessments of disease activity and patient's assessment of pain (on visual analogue scale), health assessment questionnaire – disability index (HAQ-DI), disease activity score in 28 joints (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), ACR and European League Against Rheumatism (EULAR) responses [26–30]. ACR20/50/70 response indicates at least 20/50/70% improvement in TJC68 and SJC66 and in three of the following five variables: patient's and physician's global assessments of disease activity, HAQ-DI, patient's assessment of pain, and erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) [30]. EULAR responses were assessed according to improvements in DAS score [28]. In addition, inflammatory, oxidative stress, and immunological markers were also considered when evaluating the clinical benefits of herbal preparations in RA patients.

2. Herbal Preparations in Clinical Studies

Various herbal preparations have undergone clinical investigation for their potential to treat RA. Extracts of the roots of *Tripterygium wilfordii* Hook F (Pin Yin name lei gong teng, also known as thunder god vine) have been used in the Traditional Chinese Medicine (TCM) for centuries to treat autoimmune and inflammatory conditions. The extracts demonstrated clinical efficacy in patients with RA both as monotherapy and in combination with various DMARDs. In a 6-month randomized, controlled clinical trial, patients with active RA experienced significantly greater improvements with *Tripterygium wilfordii* root extract (60 mg × 3/day) than with sulfasalazine (1 g × 2/day), a widely used conventional DMARD [31]. The extract, obtained by sequential extraction of powdered roots with ethanol and ethyl acetate, was standardized in triptolide and tripdiolide (60 mg of extract contained a total of 30 μg from both compounds combined) [32]. The improvements were evaluated based on the percentages of patients achieving ACR20, ACR50, and ACR70 responses, HAQ score, number of tender and swollen joints, pain intensity, patient's and physician's global assessments of disease activity, ESR, CRP, interleukin (IL)-6, and rheumatoid factor (RF) [31]. It is worth emphasizing that *Tripterygium wilfordii* root extract caused more pronounced reductions compared to sulfasalazine in the plasma levels of IL-6, an indicator of cartilage loss and RF, an indicator of autoimmune conditions [31,33,34]. Moreover, patients treated with the extract reported significantly fewer adverse effects compared to those receiving sulfasalazine; the most commonly mentioned adverse effects by extract-treated patients were gastrointestinal events [31]. Combining *Tripterygium wilfordii* root extract with methotrexate boosted the clinical efficacy of the latter. In a 6-month multicentre, open-label, randomized, controlled clinical study, a combination of *Tripterygium wilfordii* root extract (not further specified) (20 mg × 3/day) and methotrexate (from 7.5 to 12.5 mg/week within one month, then 12.5 mg/week) was better than methotrexate in terms of patients attaining ACR20, ACR50, ACR70, good or moderate EULAR responses and improvements in tender and swollen joints, patient's and physician's global assessments of disease activity, ESR, CRP, DAS28, and CDAI. In addition, extract-based monotherapy was more effective than methotrexate monotherapy (at the doses stated above) [35]. Other clinical studies demonstrated the superiority of *Tripterygium wilfordii* root extract to placebo [32] and clinical efficacy associated with the topical application of the root extract (tincture) [36]. Diterpenoids (triptolide, tripdiolide, triptonide) are the main anti-inflammatory and immunoregulatory compounds in *Tripterygium wilfordii* roots [35]. Triptolide, for example, decreased inflammatory markers (tumor necrosis factor (TNF)-alpha, IL-1beta, IL-6, matrix metalloproteinase (MMP)-3, -9) in RA-fibroblast-like synoviocytes and collagen-induced arthritis rats [37], reduced the number of osteoclasts in the inflamed joints, reduced the activation of nuclear factor kappa-B (NF-kB), and up-regulated osteoprotegerin in collagen-induced arthritis mice [38]. *Tripterygium wilfordii* extracts can induce hepatotoxicity, nephrotoxicity, gastrointestinal, reproductive, and skin toxicity. These side effects, some of them reversible when the treatment is stopped, can be mitigated by dose adjustment [38].

Total glucosides of paeony (TGP), extracted from the roots of *Paeonia lactiflora* Pallas and containing 90% paeoniflorin, is extensively used to treat RA in China. In 1998, China Food and Drug Administration approved TGP as a disease-modifying drug for RA [39]. Eight randomized controlled trials enrolling 522 RA patients evaluated the efficacy and safety of TGP in combination with methotrexate (0.3/0.6 g TGP × 3/day, 7.5–15 mg methotrexate once a week, 12/24 weeks). TGP combined with methotrexate demonstrated superior therapeutic effects compared to methotrexate alone regarding the decrease in SJC and ESR. The rate of adverse effects (mild to moderate digestive events, mild liver abnormalities) was lower in patients treated with the combination therapy [40]. Other randomized controlled trials (463 RA patients, 465 controls) support the efficacy and safety of TGP co-administration with methotrexate and leflunomide therapy in active RA. The addition of TGP (0.6–1.8 g/day) to methotrexate (7.5–15 mg/week) and leflunomide (10–20 mg/day) therapy for 12–24 weeks was more efficient in reducing ESR, CRP, and RF than methotrexate and leflunomide therapy. Both methotrexate and leflunomide are hepatotoxic and increase the risk of dyslipidemia in RA patients; the addition of TGP had positive effects on

the lipid profile and liver function [41]. Paeoniflorin, a monoterpene glucoside and the major active component of TGP, is a potent anti-inflammatory, immunomodulating, and antioxidant agent: it regulates the proliferation and activation of T and B lymphocytes, macrophages, dendritic cells, and synoviocytes, suppresses the production of inflammatory mediators (TNF-alpha, IL-1, prostaglandin E2 (PG E2)), regulates signaling pathways associated with inflammation (G protein-coupled receptor, mitogen-activated protein kinases (MAPKs), Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathways) and oxidative stress (reactive oxygen species (ROS)/p38/p53 pathway) [42].

Combined administration of a dry olive (*Olea europea* L.) leaf ethanolic (80% m/m) extract with methotrexate was more effective than methotrexate monotherapy in patients with early phase RA, but not in patients with long-term RA. The extract (190 mg of standardized extract with approximately 35 mg of oleuropein/capsule, 2 capsules × 2/day, 6 weeks) acted synergistically with methotrexate (10–17.5 mg/week) in counteracting oxidative stress (indicated by lipid peroxidation level in erythrocytes), DNA damage (expressed as number of lymphocytes with damaged DNA), and inflammatory status (assessed *via* plasma IL-6 level). This study demonstrates the capacity of the olive leaf ethanolic extract to modulate the effects of the standard methotrexate therapy and highlights the necessity of early intervention in the disease progression, before the onset of irreversible cellular damage [43]. Oleuropein, the major polyphenol in the dry olive leaf extract, is endowed with remarkable antioxidant and anti-inflammatory effects. Due to its ortho-diphenolic group, oleuropein effectively scavenges ROS. In addition, it enhances the level of both enzymatic and non-enzymatic endogenous antioxidants and significantly reduces various inflammatory mediators (IL-1beta, IL-6, NF-kB, TNF-alpha, inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), MMP-9) [44].

Garlic supplementation (500 mg dried garlic powder/tablet × 2/day equivalent to 2.5 g of fresh garlic, 2–3 mg allicin/garlic tablet, 8 weeks) in patients with active RA under treatment with DMARDs caused significant decreases in the serum levels of CRP and TNF-alpha, TJC and SJC, pain intensity, DAS28, and fatigue as compared with the placebo group. Garlic (*Allium sativum* L.) contains a wide variety of bioactive phytochemicals including organosulfur compounds (allicin, ajoene, diallyl sulphide, S-methylcysteine, S-allylcysteine, alliin), phenolic compounds (beta-resorcylic, protocatechuic, and gallic acids, pyrogallol, rutin, quercetin), amino acids, and polysaccharides [3]. Allicin, generated from alliin *via* the enzymatic activity of aliinase, has numerous pharmacological activities including anti-inflammatory activity. Allicin was reported to reduce the release of TNF-alpha, IL-1alpha, -1beta, -6, -8 and downregulate the expression of COX-2, iNOS, Cd68, and HLA-B2704 proteins both *in vitro* and *in vivo* [45].

Silymarin, a mixture of flavonolignans isolated from milk thistle (*Silybum marianum* (L.) Gaertn.) fruits with silybin (silibinin) as major component (50–70%), is extensively used for liver protection and regeneration due to its remarkable anti-inflammatory and antioxidant effects. In patients with active RA under treatment with conventional DMARDs, silymarin supplementation (300 mg/day, 8 weeks) caused significant improvements in the tender and swollen joints, pain, morning stiffness, disease activity and disability indices (DAS28, CDAI, SDAI, HAQ-DI), EULAR responses, fatigue, depression, and anxiety compared to patients treated solely with DMARDs [46]. This clinical trial confirmed the anti-inflammatory potential of silymarin demonstrated in various cell-based and animal experimental models. In IL-1beta-stimulated human primary chondrocytes, silymarin decreased pro-inflammatory cytokines (IL-1beta, TNF-alpha) and MMP-3, -9) and increased the production of tissue inhibitor of MMP-1 [47]. Silymarin showed anti-inflammatory activity in carrageenan and papaya latex-induced rat paw edema and arachidonic acid-induced mouse ear edema models and anti-arthritic activity in mycobacterial adjuvant-induced arthritis rat model [48]. In Freund's adjuvant-induced arthritis rat model, silymarin not only attenuated the increase in rat paw circumference but reduced seric RF and pro-inflammatory cytokines (TNF-alpha, IL-1beta, -17, PG E2) and increased seric anti-inflammatory cytokines (IL-4) [49].

Sea buckthorn (*Elaeagnus rhamnoides* (L.) A. Nelson syn. *Hippophaë rhamnoides* L.) fruit oil offers therapeutic benefits for various skin, mucosal, cardiovascular, liver, and metabolic conditions and ailments. It is also well-known for its capacity to attenuate the side effects of radiotherapy and chemotherapy in cancer patients [50–52]. Sea buckthorn fruit oil supplementation (900 mg × 2/day, 12 weeks) in patients with active RA under treatment with a combination of methotrexate (15 mg/week) and diclofenac sodium (50 mg/day) resulted in significant improvements in the TJC and SJC, pain, morning stiffness, patient's and physician's global assessments of disease activity, SDAI, CDAI, HAQ-DI, ACR20, ACR50, EULAR (ESR) and EULAR (CRP) responses, and serum malondialdehyde (MDA), an oxidative stress marker, compared to patients treated only with methotrexate and diclofenac sodium. Overall, sea buckthorn fruit oil supplementation significantly alleviated the swelling, pain, stiffness, and physical disability, improving the general condition of RA patients [53,54]. These benefits are undoubtedly linked to the compounds in sea buckthorn fruit oil that attenuate inflammation and oxidative stress by various mechanisms: oleic acid inhibits NF-kB, TNF-alpha, IL-6, and -12 release, COX-2, iNOS and activates

heme oxygenase-1 (HO-1), glutathione peroxidase (GPx), superoxide dismutase (SOD), and IL-10 release [55], palmitoleic acid reduces the production of TNF-alpha, interferon (IFN)-gamma, IL-2, -6, -17A and inhibits NF-kB and lipid peroxidation [56,57], carotenoids, tocopherols and sitosterols suppress iNOS, COX-2, NF-kB, TNF-alpha, IL-1beta, -6, -8, and lipid peroxidation while upregulating IL-10 [58–63].

In a double-blind randomized clinical trial, pomegranate (*Punica granatum* L.) extract (solvent not specified) supplementation (2 capsules of 250 mg extract/day, 8 weeks) significantly reduced the SJC and TJC, pain intensity, morning stiffness, DAS28 and HAQ scores, ESR, and increased GPx level compared with placebo in RA patients receiving standard medications (methotrexate, prednisolone, hydroxychloroquine, sulfasalazine, NSAIDs). The extract contained 40% ellagic acid [64]. The latter exhibits anti-inflammatory activity mediated mainly through the inhibition of NF-kB pathway with consequent downregulation of pro-inflammatory iNOS, COX-2, TNF-alpha, and IL-6 [65]. The anti-inflammatory activity of the investigated pomegranate extract is not solely attributed to ellagic acid and other polyphenols. Pomegranate has a positive impact on the gut microbiota, the latter playing a key role in the pathogenesis of RA [64]. RA patients have reduced fecal load of *Bifidobacterium* and *Bacteroides* species [66]. Pomegranate extract was reported to increase the abundance of bifidobacteria in the cecum [64].

A 90-day clinical study, including 41 women diagnosed with RA and treated with steroids and one or two DMARDs, demonstrated clear benefits (significant reduction in DAS28 score and anti-cyclic citrullinated peptide (anti-CCP) antibodies - diagnosis and prognosis markers in RA) for the ingestion of 500 mL/day of low calorie cranberry (*Vaccinium macrocarpon* Aiton) juice. Among cranberry juice components, quercetin and resveratrol play a major role in its anti-inflammatory activity. Both compounds downregulate NF-kB pathway. In addition, quercetin inhibits pro-inflammatory enzymes (COX, lipoxygenase) while resveratrol modulates JAK STAT3 pathway [67].

Administration of a highly purified aqueous extract from the pentacyclic chemotype of cat's claw (*Uncaria tomentosa* (Willd.) DC.) demonstrated favorable effects in RA patients under treatment with sulfasalazine or hydroxychloroquine. The extract (14.7 mg/g pentacyclic oxindole alkaloids, no tetracyclic oxindole alkaloids) was administered at a daily dose of 60 mg (20 mg × 3/day). In this 2-phase study (52 weeks), the extract reduced the number of painful and swollen joints and Ritchie index, the latter assessing joint tenderness and disease severity. The plant has been traditionally used to treat rheumatic diseases in Peru. The therapeutic properties of the plant are partly attributed to its pentacyclic oxindole alkaloids. These compounds have immunomodulatory effects (inhibition of activated lymphocytes proliferation and activation of resting/weakly activated lymphocytes proliferation, both effects being antagonized by the tetracyclic oxindole alkaloids). In addition, pentacyclic oxindole alkaloids suppress the production of TNF-alpha and mitigate oxidative stress [68].

A standardized rose hip (*Rosa canina* L.) powder showed benefits in patients with RA undergoing various treatments (NSAIDs, steroids, DMARDs). More specifically, 5 g of rose hip powder daily (5 capsules × 2/day, 0.5 g of powder/capsule, 6 months) substantially improved the physical ability and general condition of the patients as indicated by HAQ-DI, patient's and physician's global assessments of disease activity, short form (SF)-12 and RA-specific quality of life (RAQoL) scores. These positive outcomes were mainly attributed to a galacto-lipid that has structure similarities with gamma-linolenic acid, a well-known anti-inflammatory agent [69]. The rose hip powder was obtained from mature fruits of plants grown in standardized fields. Optimal fruits were dried below 40 °C, powdered, and controlled regarding mineral and vitamin content [70].

The main outcomes of the referenced clinical studies are given in detail in Table 1.

Table 1. Evidence from clinical studies on herbal preparations as alternative to or support for standard therapy in rheumatoid arthritis.

Nr.	Type of Clinical Study	Nr. Patients	Part of Plant/Extract	Administration	Outcomes	Ref.
1.	multicentre, double-blind, randomized, controlled	121	*Tripterygium wilfordii* ethanol/ethyl acetate root extract	extract (60 mg × 3/day) *vs*. sulfasalazine (1 g × 2/day); 6 months	ACR20 response: 65.0% *vs*. 32.8%; ACR50 response: 33.3% *vs*. 4.9%; ACR70 response: 16.7% *vs*. 1.6%; decrease in HAQ score: 0.60 *vs*. 0.22; decrease in IL-6 (pg/mL): 24.81 *vs*. 4.63; decrease in RF (IU/mL): 483.77 *vs*. 152.59	[31]
2.	multicentre, open-label, randomized, controlled	207	*Tripterygium wilfordii* root extract	extract (20 mg × 3/day) *vs*. methotrexate (from 7.5 to 12.5 mg/week within one month, then 12.5 mg/week) *vs*. extract plus methotrexate (same doses mentioned above); 6 months	ACR20 responses: 72.5% *vs*. 63.8% *vs*. 92.8%; ACR50 responses: 55.1% *vs*. 46.4% *vs*. 76.8%; ACR70 responses: 30.4% *vs*. 23.2% *vs*. 43.5%; CDAI good responses: 65.2% *vs*. 52.2% *vs*. 87.0%; EULAR good responses: 47.8% *vs*. 26.1% *vs*. 58.0%; ESR (mm/h): 21.2 *vs*. 27.6 *vs*. 17.4; CRP (mg/L): 9.4 *vs*. 15.2 *vs*. 7.8; DAS28: 3.57 *vs*. 4.03 *vs*. 3.19	[35]
3.	randomized, controlled (meta-analysis of 8 studies)	522	TGP	TGP (0.3/0.6 g × 3/day) plus methotrexate (7.5-15 mg once a week) *vs*. methotrexate (same doses mentioned above); 12/24 weeks	more significant decrease in ESR and SJC in TGP plus methotrexate group *vs*. methotrexate group	[40]
4.	randomized, controlled (meta-analysis of 8 studies)	928	TGP	TGP (0.6-1.8 g/day) plus methotrexate (7.5-15 mg once a week) plus leflunomide (10-20 mg/day) *vs*. methotrexate plus leflunomide (same doses mentioned above); 12-24 weeks	more significant decrease in ESR, CRP and RF in TGP plus methotrexate plus leflunomide group *vs*. methotrexate plus leflunomide group	[41]
5.	randomized, controlled	32	*Olea europea* leaf ethanolic (80% m/m) extract	extract (380 mg × 2/day) plus methotrexate (10-17.5 mg/week) *vs*. methotrexate (same doses mentioned above); 6 weeks	lymphocytes with damaged DNA: 7.33 *vs*. 22.84 (in early phase RA patients)	[43]
6.	randomized, double-blind, placebo controlled	70	*Allium sativum* dried powder	dried powder (500 mg × 2/day) plus DMARDs *vs*. placebo plus DMARDs; 8 weeks	CRP (mg/L): 8.62 *vs*. 14.23; TNF-alpha (ng/L): 19.04 *vs*. 32.10; pain intensity (mm): 59.35 *vs*. 69.19; TJC28: 3.61 *vs*. 5.55; DAS28: 3.80 *vs*. 4.45; fatigue: 30.90 *vs*. 37.64	[3]
7.	randomized, controlled	122	silymarin	silymarin (300 mg/day) plus DMARDs *vs*. DMARDs; 8 weeks	TJC28: 9.58 *vs*. 21.38; SJC28: 3.97 *vs*. 13.57; pain (cm): 3.56 *vs*. 7.88; morning stiffness (min): 27.97 *vs*. 38.93; DAS28 (ESR): 4.82 *vs*. 6.82; DAS28 (CRP): 4.42 *vs*. 6.41; CDAI: 20.37 *vs*. 50.77; SDAI: 21.44 *vs*. 52.17; HAQ-DI: 1.18 *vs*. 2.17;	[46]

					EULAR good responses: 83.05% *vs.* 1.79%; fatigue (VAS-F): 37.80 *vs.* 75.36; depression (BDI-II): 8.90 *vs.* 21.21; anxiety (GAD-7): 3.54 *vs.* 12.12	
8.	randomized, controlled	80	*Hippophaë rhamnoides* fruit oil	fruit oil (900 mg × 2/day) plus methotrexate (15 mg/week) plus diclofenac sodium (50 mg/day) *vs.* methotrexate plus diclofenac sodium (same doses mentioned above); 12 weeks	TJC28: 12.21 *vs.* 20.43; SJC28: 5.81 *vs.* 13.05; pain (cm): 3.16 *vs.* 7.35; morning stiffness (min): 21.62 *vs.* 45.12; DAS28 (ESR): 5.31 *vs.* 6.68; DAS28 (CRP): 4.66 *vs.* 6.21; CDAI: 24.35 *vs.* 48.17; SDAI: 25.13 *vs.* 49.56; HAQ-DI: 1.05 *vs.* 1.91; EULAR (ESR) good responses: 35.1% *vs.* 0%; EULAR (CRP) good responses: 59.5% *vs.* 0%	[53, 54]
9.	randomized, double-blind, placebo controlled	55	*Punica granatum* extract	extract (250 mg × 2/day) plus standard medications *vs.* placebo plus standard medications; 8 weeks	swollen joints: decrease by 2.6 *vs.* increase by 0.08; tender joints: decrease by 2.1 *vs.* increase by 0.9; pain (mm): decrease by 17.6 *vs.* decrease by 1.6; morning stiffness (min): decrease by 36.01 *vs.* increase by 0.0; DAS28: decrease by 0.9 *vs.* increase by 0.1; HAQ: decrease by 0.4 *vs.* decrease by 0.1; ESR (mm/h): decrease by 4.3 *vs.* increase by 3.5; GPx (nmoL/mL/min): increase by 18.3 *vs.* decrease by 1.6	[64]
10.	randomized, controlled	41	*Vaccinium macrocarpon* juice	juice (500 mL/day) plus standard medications *vs.* standard medications; 90 days	DAS28: 2.99 *vs.* 3.52; anti-CCP antibodies (U/mL): 0.9 *vs.* 5.55	[67]
11.	randomized, double-blind, placebo-controlled, two-phase	40	*Uncaria tomentosa* aqueous extract	1-phase: extract (20 mg × 3/day) plus sulfasalazine or hydroxychloroquine *vs.* placebo plus sulfasalazine or hydroxychloroquine; 24 weeks 2-phase: extract (20 mg × 3/day) plus sulfasalazine or hydroxychloroquine; 28 weeks	1-phase, painful joints: decrease by 53.2% *vs.* decrease by 24.1% 2-phase, significant reductions in the painful and tender joints and Ritchie index in patients receiving extract only in phase-2 *vs.* patients receiving placebo in phase-1	[68]
12.	randomized, double-blind, placebo-controlled, parallel	89	*Rosa canina* standardized powder	dried powder (2.5 g × 2/day) plus standard medications *vs.* placebo plus standard medications; 6 months	HAQ-DI: 1.03 *vs.* 1.15; DAS28: 3.93 *vs.* 4.42; RAQol: 10.18 *vs.* 11.09; SF-12 physical: 36.22 *vs.* 33.78	[69]

ACR - American College of Rheumatology; anti-CCP - anti-Cyclic Citrullinated Peptide antibodies; BDI-II - Beck Depression Inventory scale II; CDAI - Clinical Disease Activity Index; CRP - C-reactive Protein; DAS28 - Disease Activity Score (in 28 joints); DMARDs - Disease-Modifying Antirheumatic Drugs; DNA - Deoxyribonucleic Acid; ESR - Erythrocyte Sedimentation Rate; EULAR - European League Against Rheumatism; GAD-7 - Generalized Anxiety Disorder-7; GPx - Glutathione Peroxidase; HAQ - Health Assessment Questionnaire; HAQ-DI - Health Assessment Questionnaire – Disability Index; IL-6 – Interleukin-6; RA - Rheumatoid Arthritis; RAQol - Rheumatoid Arthritis - specific Quality of life; RF - Rheumatoid Factor; SDAI -

Simplified Disease Activity Index; SF - Short Form; SJC – Swollen Joint Count; TGP - Total Glucosides of Paeony; TJC - Tender Joint Count; TNF-alpha - Tumor Necrosis Factor-alpha; VAS-F - Visual Analogue Scale-Fatigue.

3. Conclusion

The clinical studies completed so far demonstrate positive outcomes for the herbal preparations as alternative or complementary therapy in patients with RA. Further multicentre research enrolling larger patient cohorts is needed to confirm these findings and establish the optimal dosage regimen to achieve the best treatment outcomes with minimal side effects. Moreover, the mechanisms that contribute to the synergistic interaction between herbal preparations and conventional treatment should be explored.

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