Herbs for Rheumatoid Arthritis

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Abstract

Numerous herbs have been studied in patients with rheumatoid arthritis. Here, use of many of these, including *Oenothera biennis* (evening primrose), *Ribes nigra* (blackcurrant), and *Borago officinalis* (borage) seed oils, *Harpagophytum procumbens*, and to a lesser extent *H. zeyheri* (African devil's club), *Tanacetum parthenium* (feverfew) herb, *Populus tremula* (European aspen), *Solidago virgaurea* (goldenrod), *Fraxinus excelsior* (European ash), *Salix* spp. (willow), *Cimicifuga racemosa* (black cohosh), *Smilax* spp. (sarsaparilla), and *Guaiacum officinale* (lignum vitae), alone and in various formulations, are discussed. *Withania somnifera* (ashwagandha), *Boswellia serrata* (frankincense), *Curcuma longa* (turmeric), *Nigella sativa* (black cumin), *Tinospora cordifolia* (guduchi), *Tribulus terrestris* (caltrop vine, gokshura), Sān Miào Săn (Three Wonder Powder), *Capsicum frutescens* (cayenne), *Allium sativum* (garlic), *Paeonia lactiflora* (white peony), *Clematis mandshurica* (clematis, wshuricahura), *Trichosanthes kirilowii* (trichosanthes, guowiia), Sān Miào *Prunella vulgaris* (heal-all), and san huang wu ji formula are also discussed in depth. The article ends with a discussion of the unusual immunosuppressive herb *Tripterygium wilfordii* (thunder duke vine).

Keywords: rheumatoid arthritis, herbal medicine, immunomodulating herbs, inflammation-modulating herbs, *Tripterygium wilfordii*

Introduction

The natural approach to patients with rheumatoid arthritis (RA) involves many components, including lifestyle changes and, as will be focused on here, herbal medicine. Botanical therapies are generally not used by themselves to remedy RA, though they do play a useful part in most treatment protocols, by both reducing symptoms and treating underlying causes.

RA commences with inflammation and hypertrophy of the synovial membrane lining various synovial joints, and thus might be better termed "rheumatoid synovitis." For unknown reasons, the distal interphalangeal joints are spared in RA, as is most of the spine, except the atlantoaxial joint. Over time, pannus forms, which is an inflammatory membrane, and that proceeds to widespread joint destruction. Mild morning stiffness and mild pain give way to major stiffness, severe pain, and joint deformities as the disease progresses. Extra-articular inflammation is also present, resulting in a reduction in lifespan, particularly due to increased cardiovascular mortality and respiratory mortality.[1] Patients who were rheumatoid factor positive (mainly immunoglobulin M antibodies reactive against immunoglobulin G antibodies) had the greatest risk of early death in this same study, with an additional increase in death due to respiratory disease.[1]

RA exhibits classic features of a multifactorial disease, with no single entity having been identified as a definitive cause. Poorly understood genetic susceptibilities allow a variety of environmental factors to provoke the disease. Lifestyle changes are important to address these environmental factors that might precipitate the disease, including stopping smoking where relevant, and periodic fasting, a vegetarian diet, probiotics supplements or increased intake of fermented foods, and/or an elimination/challenge diet to identify and remove possible food triggers.[2–4]

Inflammation Modulating Herbs

Several herbs have been shown to modulate inflammation in patients with RA. The concept of inflammation modulation (as opposed to anti-inflammatory) as related to herbal medicine has been discussed previously in detail.[5] Briefly, these herbs do not simply suppress a single inflammatory pathway but usually affect multiple immunological pathways, resulting in a lowering of "inflammatory tone" in the body. This differs from most anti-inflammatory drugs that more strongly suppress one immune pathway, sometimes resulting in quicker and more potent resolution of symptoms but at the cost of significantly greater and more serious adverse effects, such as promotion of malignancies or reactivation of latent infections. Inflammation-modulating herbs might represent treatment that truly addresses underlying causes of RA, or they may help mitigate the pathology and symptoms—thus buying time for conventional disease-modifying approaches to work: which exactly has not been determined. The diversity of mechanisms behind their inflammation modulation, and possibly their potency, differentiates these herbs from pharmaceuticals and helps explain the slower but safer effects of them in RA patients.

A meta-analysis of 19 double-blind, randomized, placebo-controlled trials of herbal inflammation modulators for RA patients found that overall they reduced symptoms (as captured in the Disease Activity Score and similar measures that assess joint stiffness, pain, and inflammation among others) compared to placebo.[6] This analysis of an extremely wide range of treatments found that omega 6 γ-linolenic acid (GLA)-rich herbs *Oenothera biennis* (evening primrose), *Ribes nigra* (blackcurrant), and *Borago officinalis* (borage) seed oils, the bitter herb *Harpagophytum procumbens*, and to a lesser extent *H. zeyheri* (African devil's club) root, *Tanacetum parthenium* (feverfew) herb, a formula containing *Populus tremula* (European aspen), *Solidago virgaurea* (goldenrod), and *Fraxinus excelsior* (European ash), and a formula containing *Salix alba* (white willow) bark, *Cimicifuga racemosa* (black cohosh) root, *Smilax* spp. (sarsaparilla) root bark, *Guaiacum officinale* (lignum vitae) resin, and European aspen bark all showed promise. Strangely, the analysis included some studies that only appeared to involve patients with osteoarthritis, which would seemingly skew the results, since RA and osteoarthritis are such distinctly different conditions. White willow bark, African devil's club, and a combination formula featuring *Withania somnifera* (ashwagandha) root, *Boswellia serrata* (frankincense) resin, *Curcuma longa* (turmeric) rhizome, and zinc were the three products assessed for osteoarthritis, so they should not have been included in the meta-analysis. It is also important to note that lignum vitae is an endangered species. Non-cultivated sources should never be used.

GLA-rich herbs are proposed to counter inflammation because they are precursors to dihomo-GLA (DGLA), an essential omega 6 fatty acid. In immune cells, DGLA is converted into the mostly beneficial, inflammation-downregulating series 1 prostaglandins. However, a small percentage of DGLA can also be converted in the liver to arachidonic acid, which is the mostly pro-inflammatory precursor to various series 2 prostaglandins and series 4 leukotrienes. An additional problem with GLA-rich herbs is that modern diets typically contain enormous quantities of linoleic acid (from vegetable oils used in fried and processed foods), which is the omega 6 fatty acid precursor to GLA.[7] This rise in linoleic acid intake is directly correlated to higher all-cause and cardiovascular mortality according to a meta-analysis.[8] It is hard to fathom logically how giving GLA could have any positive effect in the face of such large linoleic acid intake. Most of the trials on evening primrose oil for various conditions are also complicated by the fact that they were funded by Scotia Pharmaceuticals, who makes the evening primrose oil product studied, and many of which were never published.[9] Nevertheless, a meta-analysis of seven clinical trials of various GLA-rich plant oils found moderate evidence for them in relieving RA symptoms.[10] A more recent open, randomized trial in 60 Serbian women with RA all taking methotrexate, <10 mg corticosteroids per day, and folic acid found that evening primrose oil (providing 334 mg GLA per day) combined with 2 g of fish oil per day or just 5 g fish oil per day were equally effective at reducing disease activity compared to patients receiving only drug therapy.[11] This contradicts the earlier case series of 12 healthy adults that found 3 mg of eicosapentaenoic acid (EPA) from fish oil per day could prevent conversion of 3 g of GLA per day to DGLA, while GLA by itself significantly raised arachidonic acid levels.[12] Oxidative stress markers were reduced by supplementation of either type of oil in the cohort of 60 Serbian women compared to patients receiving only conventional therapy.[13] GLA-rich oils are not associated with any common, serious adverse effects and do not cause more mild adverse effects than placebo in controlled trials. This coupled with some positive results in clinical trials suggests the conversion of some GLA into arachidonic acid may not be clinically relevant, but much more work is needed to determine if this is true. It is also an open question whether a combination of various essential fatty acids (GLA, fish oil, DGLA, and/or others) with other agents would be beneficial.

The appropriate dose of GLA-rich botanical oils, if they are to be used at all, is confusing. While various trials using a low dose of GLA (<500 mg/day) report benefits in some studies, another meta-analysis of trials of GLA-rich oils in RA patients found that only those that supplemented at least 1,400 mg of GLA daily showed benefit.[14] Most of these plant oils are only 9% GLA at most, and so most available sources of these oils require taking at least 15 g per day to achieve therapeutic GLA doses. This makes such therapy moderately expensive and would require taking a large number of capsules per day (as most available products contain 1 g of oil per capsule). However, some products contain up to 20–25% GLA and would require fewer capsules or teaspoonfuls of oil to achieve therapeutic doses.

Nigella sativa (black cumin) seed oil is another potential remedy for RA patients based on its fatty acid and terpenoid content. This plant, in the Ranunculaceae family, is a major medicine across Asia and has previously been reviewed in depth in this journal.[15] Based on its historical use, inflammation-modulating properties, and early animal studies suggesting it could help RA, a clinical trial was conducted.[16,17] In this trial, 40 Egyptian women with RA first took placebo bid for one month followed by 500 mg of cold-pressed black cumin oil bid for one month.[18] All subjects were concomitantly taking methotrexate, folic acid, hydroxychloroquine, and diclofenac throughout the trial. The disease activity score was significantly lower after the black cumin oil phase compared to after the placebo phase. There was no negative interaction with concomitant medications and no significant adverse effects. A more rigorous double-blind trial in 43 Iranian women with RA randomized them to take placebo or 500 mg of black cumin oil b.i.d. for two months.[19] Disease activity was again reduced significantly in the black cumin oil group compared to placebo, as was the highly sensitive C-reactive protein level. Modulation of T-helper lymphocytes and increased functional activity of natural killer cells were demonstrated to play at least a partial role in the efficacy of black cumin oil. Given the safety and preliminary efficacy of this therapy, it can be recommended as a long-term immunomodulating and inflammation-modulating therapy for RA patients.

African devil's claw is a member of the Pedaliaceae family, an unusual botanical family that includes sesame. Clinical trials are mixed on its benefits for RA patients, though the meta-analysis cited above concluded it was overall beneficial.[6] Its fruits are covered in rounded claw-like structures, hence its name. American devil's claw (*Proboscidea parviflora* and related species) is unlikely to be confused, as it is mostly used for weaving and not medicine, but devil's club (*Oplopanax horridum*) could be confused based on common name, though it is an immunomodulator and antidiabetic herb and so fairly unlike African devil's claw. African devil's claw is native to the Kalahari desert of southern Africa, and overharvesting for medicine had been such a growing problem, it was proposed to be listed in the Convention on International Trade in Endangered Species (CITES) in 2000.[20] This led to a concerted effort by the government of Namibia in particular both to better train wild harvesters and to increase cultivation. This effort was considered sufficiently successful that the proposed CITES listing was dropped in 2004. Nevertheless, given how far away the plant has to travel to get to North America and the existence of many alternatives, it seems ecologically unwise to use African devil's claw on this continent.

Another well-known inflammation modulator is *Salix* spp. (willow) in the Salicaceae family. *Populus* spp. (cottonwood, aspen) are another group of trees in this family with very similar chemistry and activity. Though *Salix alba* (white willow) is frequently cited as the species used, an analysis of the content of salicylate glycosides, principally salicin, in the bark of this species was significantly lower than that found in other European species such as *S. daphnoides* (European violet willow), a hybrid of *S. integra* × *S. kochiana*, and *S. purpurea* (purple willow).[21] It has long been known that a range of human gut flora are crucial in activating salicylate glycosides by hydrolyzing the glycone.[22]

Willow, cottonwood, and aspen bark were all historically used for RA and other painful autoimmune diseases.[23] The only modern clinical trial that appears to have assessed the efficacy of willow bark by itself randomized 26 RA patients to a European violet willow extract containing 240 mg of salicin per day or placebo for six weeks.[24] Assessed by patients' ratings of their pain on a visual analog scale, the extract was no more effective than placebo at reducing pain. On average, the willow extract reduced pain by 15%. There was no difference between willow and placebo in terms of adverse effects. While of course it is possible willow failed because it is not effective for RA, it is also possible the small sample size, short duration of the trial, dose, or specific extract used could have played a role.

Two European herbal formulas containing salicylate-rich herbs have been studied in RA patients. The best studied is known by the trade name Phytodolor® (from the Latin for herb and pain; Steigerwald Arzneimittel GmbH, Darmstadt, Germany), also known as STW1, and contains *Populus tremula* (European aspen), *Solidago virgaurea* (goldenrod), and *Fraxinus excelsior* (European ash). The exact ratios of each plant present are unknown, but it is standardized to provide 0.75 mg/mL of salicin, 0.042 mg/mL of salicylic alcohol, 0.015 mg/mL of isofraxidin, and 0.06 mg/mL of rutin, and the usual dose is 1 mL three to four times per day. A simple combination of equal parts of the three herbs seems appropriate for creating an approximation of the formula, which was not available commercially in North America at the time of publication.

A meta-analysis of 11 clinical trials of Phytodolor® for all manner of musculoskeletal disorders concluded it was effective compared to placebo, particularly in the subgroup with rheumatic pain and other conditions besides osteoarthritis.[25] It has been shown to be as effective for pain relief as piroxicam and diclofenac, and to reduce the need for rescue pain medication. Given its excellent safety record, this formula seems appropriate for clinical use.

Another formula, known by the trade name Reumalex®, contains 100 mg of white willow bark along with 40 mg of *Guaiacum officinale* (lignum vitae) resin, 35 mg of *Cimicifuga racemosa* (black cohosh) root, 25 mg of *Smilax* spp. (sarsaparilla) root bark, and 25 mg of *Populus tremula* (European aspen) bark per tablet. In a double-blind randomized trial of 82 British subjects, some of whom had RA, an undisclosed dose of the formula was superior to placebo at relieving joint pain after two months of treatment. Patients were still able to take prior analgesic medications, and there was no change in use of these drugs between the groups. The inability to analyze the RA patients' data separately from that of patients with other kinds of arthritis, the lack of a stated dose, and lack of difference in concomitant analgesic use all weaken the conclusions of this trial substantially. Additionally, as previously mentioned, lignum vitae is of dubious ecological sustainability, given current harvesting methods and its limited distribution, all suggesting this formula should not be used until more research is done and sourcing is proven harmless.

The above inflammation-modulating herbs are worth considering as at least an adjunct to conventional treatment of RA patients. Others have been studied for this purpose, sometimes having no effect at the dose and form used and sometimes showing preliminary promise. A collection of such herbs are reviewed in Table 1.

Immunomodulating Herbs

RA is of course an autoimmune disorder, and so treatments that can interrupt this attack on synovial and other cells by the patient's own immune cells are crucial to treating the roots of the conditions. Quite a few herbs have been shown to help patients with RA and to have immunomodulating effects, mainly by affecting T-lymphocyte activity. Since these cells, along with dendritic and antigen-presenting cells, are the prime regulators of the entire immune system, affecting them can lead to profound effects throughout the body. However, there have been few studies of herbs in this category. Those that have been published to date have been largely disappointing.

Table 1. Other Inflammation-Modulating Herbs for Rheumatoid Arthritis: Results of Clinical Trials

Herb(s) or extract	Clinical trial results
Tanacetum parthenium (feverfew) leaf	Negative double-blind, placebo-controlled clinical trial in 40 British RA patients[a]
Zingiber officinale (ginger) rhizome	Open trial in 28 Danish RA patients found benefit[b]; see also combination studies with *Withania somnifera* discussed in body of text
Boswellia serrata (frankincense) resin	Negative double-blind trial in 37 German RA patients[c]; see also combination studies with *Withania somnifera* discussed in body of text
Curcuma longa (turmeric); extract of isolated curcumin	Double-blind, randomized trial found 500 mg b.i.d. of curcumin, 50 mg b.i.d. of diclofenac, and their combination equally effective in 45 Indian RA patients; curcumin was safer[d]; see also combination studies with *Withania somnifera* discussed in body of text
Mangifera indica (mango) stem bark extract	Adding 300 mg t.i.d. to methotrexate (sometimes with NSAIDs or prednisone) was superior to these drugs alone for reducing disease activity in randomized six-month trial[e]
Humulus lupulus (hops) iso-alpha-acids, *Rosmarinus officinalis* (rosemary) leaf extract, oleanolic acid	A dose of 440 mg t.i.d. reduced pain in an open trial[f]

[a]Pattrick M, Heptinstall S, Doherty M. Feverfew in rheumatoid arthritis: A double blind, placebo controlled study. Ann Rheum Dis 1989;48:547–549.
[b]Srivastava KC, Mustafa T. Ginger (*Zingiber officinale*) in rheumatism and musculoskeletal disorders. Med Hypoth 1992;39:342–348.
[c]Sander O, Herborn G, Rau R. Is H15 (resin extract of *Boswellia serrata*, "incense") a useful supplement to established drug therapy of chronic polyarthritis? Results of a double-blind pilot study. Z Rheumatol 1998;57:11–16 [in German].
[d]Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res 2012;26:1719–1725.
[e]López Mantecón AM, Garrido G, Delgado-Hernández R, Garrido-Suárez BB. Combination of *Mangifera indica* L extract supplementation plus methotrexate in rheumatoid arthritis patients: A pilot study. Phytother Res 2014;28:1163–1172.
[f]Lukaczer D, Darland G, Tripp M, et al. A pilot trial evaluating Meta050, a proprietary combination of reduced iso-alpha acids, rosemary extract and oleanolic acid in patients with arthritis and fibromyalgia. Phytother Res 2005;19:864–869.
RA, rheumatoid arthritis; NSAIDs, nonsteroidal anti-inflammatory drugs.

Withania somnifera (ashwagandha) root is a traditional Indian herb in the Solanaceae family known to be an immune and inflammation modulator.[26] It has a strong traditional reputation for helping RA. While it has not been studied alone, trials looking at formulas featuring this herb in RA have been published. An early, double-blind clinical trial randomized 182 Indian RA patients to take either a combination of ashwagandha, *Boswellia serrata* (frankincense) resin, *Zingiber officinale* (ginger) rhizome, and *Curcuma longa* (turmeric) rhizome or placebo for four months.[27] Exact ratios of the herbs and doses are unknown. There was no difference between the groups in improvement in American College of Rheumatology (ACR) symptom criteria, a common measure of efficacy in RA clinical trials. There was an extraordinarily strong placebo response in this trial. Only patients with swollen joints and with positive rheumatoid factor levels were significantly improved by the herbal formula compared to placebo. Safety was very good.

A more recent trial looked at a formula containing ashwagandha, ginger, *Tinospora cordifolia* (guduchi), and *Tribulus terrestris* (caltrop vine, gokshura) herb. This trial randomized 121 Indian RA patients to either the herbal formula two capsules b.i.d. (providing 750 mg total daily dose), the single Ayurvedic herb *Semecarpus anacardium* (bhallaatak, marking nut) treated with *Shorea robusta* (shala tree) resin to reduce its general toxicity (dose unstated), or 200 mg b.i.d. of hydroxychloroquine in a single-blind manner for six months.[28] Again, the ratios of the herbs in the formula were not disclosed. None of the patients in this trial had taken immunosuppressive medications in the past six months. There was no difference between the groups in terms of how many subjects achieved at least a 20% reduction in ACR symptom score, suggesting both herbs were as effective as hydroxychloroquine. Joint count pain tenderness, pain visual analog scale, and several other efficacy measures indicated that the herbal formula was superior to bhallaatak. All three treatments were very safe.

Ganoderma lucidum (reishi, líng zhī) is an immunomodulating mushroom, long revered in Asian traditional medicine.[29] Two clinical trials have evaluated the use of reishi along with the Chinese herbal formula Sān Miào Sǎn (Three Wonder Powder; see Table 2), originated in *Fang's Orthodox Lineage of Pulse and Symptoms* (Fāng Shì Mài Zhèng Zhèng Zōng) in 1749 by Fāng Zhào-Quán, for RA patients.

The older trial involved 65 Chinese RA patients and was not described as randomized or double-blind, but half the group took placebo while the other half took 10 g/of day reishi powder and Three Wonder Powder, delivering 6 g of each of its three ingredients per day for six months.[30] Ex vivo stimulation of peripheral blood mononuclear cells from patients taking the

Table 2. Sān Miào Sǎn (Three Wonder Powder)

Herb	Part used
Phellodendron amurense (Amur cork tree, huáng bǎi)	Bark[a]
Atractylodes chinensis (black atractylodes, cāng zhú)	Root
Achyranthes bidentata (ox knee)	Root

[a]Original formula called for wine-fried bark; it is not clear if this is what was used in the clinical trials.

herbal mixture showed a significant reduction in interleukin-18 production compared to the placebo group. None of the other measures of immune activity was altered in this trial. Note that patients continued to take a wide array of conventional medications during this trial in both groups.

A later and more useful trial also randomized 65 Chinese RA patients to the same herbal combination or placebo for six months.[31] This trial was explicitly stated to be double-blind, and patients were also taking an array of conventional medications. The doses used were 4 g of reishi and 2.4 g of each of the ingredients in Three Wonder Powder per day. It is possible this was the same trial as the one described above, as the sample size and duration were similar, but the doses delivered were clearly different. There was no difference between the two groups in terms of how many achieved at least a 20% reduction in the ACR symptom score. Pain was significantly reduced in the herbal group, though it was unclear if this was compared to baseline or the placebo group. The safety of the herbal mixture was excellent.

Andrographis paniculata (andrographis, kalmegh) aerial parts are an important Asian traditional medicine in the Acanthaceae family. It is extremely bitter (earning it another common English name, king of bitters). It has often been called, including by this author, an immune stimulant, based in large part on its benefits for patients with acute respiratory infections.[32] However, mechanistic studies consistently have shown that this herb is immunomodulating and does not simply increase immune activity.[33,34] It is also inflammation modulating, with effects that include inhibition of NF-κB activation.[35]

A double-blind trial randomized 60 Chilean RA patients to an extract of andrographis providing 30 mg of andrographolides t.i.d. or placebo for 14 weeks.[36] All patients were on methotrexate and were also allowed to be on corticosteroids or hydroxychloroquine, but no nonsteroidal anti-inflammatory drugs (NSAIDs) were allowed. There was no difference between the andrographis and placebo group in the primary outcome of visual analog pain scale, but number and severity of swollen, tender joints decreased significantly with the herbal treatment over controls. Rheumatoid factor levels fell significantly with andrographis treatment compared to placebo. Adverse effects were mild and not different from the placebo group. As with other trials noted here, this suggests that the effects of andrographis are relatively mild in patients already on one or more disease-modifying drugs. A more interesting trial would look at patients not yet on such drugs or in direct comparison to them to see if andrographis would work equally as well.

Spicy Relief

Capsicum frutescens (cayenne) fruit is a familiar, spicy member of the Solanaceae family, in large part due to the compound capsaicin. Topical application of cayenne extracts and pure capsaicin have been investigated as an analgesic in arthritis patients. This is a particularly important alternative for pain relief, given the known complications from long-term NSAID use in RA patients, including peptic ulcer, gastrointestinal bleeding, and kidney damage. In the first double-blind trial, 31 American RA patients were randomized to apply either a 0.025% capsaicin cream four times daily or placebo for four weeks to painful knees.[37] Pain relief was significantly greater with capsaicin than placebo. Transient burning at the application site was noted in about half the treated patients. Usually this passes with recurrent use, but not always. No other adverse effects were noted.

A separate clinical trial tested a 0.075% capsaicin cream in just seven American RA patients with hand pain.[38] They were again randomized to capsaicin applied four times daily or placebo in a double-blind fashion for four weeks. There was no benefit from capsaicin compared to placebo in this trial. Its much smaller sample size could easily have contributed to the negative outcome. Larger, more rigorous trials are necessary to confirm the benefits of capsaicin or crude cayenne topical applications for pain control.

One small open trial has assessed the potential value of *Allium sativum* (garlic) extract in patients with RA, a different pungent herb. In this study, 30 Russian RA patients all taking disease-modifying drugs were randomized to either add 300 mg b.i.d. of garlic extract or no additional therapy for four to six weeks.[39] A total of 87% of the garlic group achieved at least a partial response, but no statistical analysis was provided comparing this to results in the drug-only group. Given the lack of adverse effects, this does at least support the safety of garlic in combination with older immunosuppressive drugs in RA. Further, rigorous studies are warranted to assess better the potential of garlic to help RA patients.

Miscellaneous Chinese Herbs

The Chinese herb *Paeonia lactiflora* (white peony, bái sháo) root without bark, in the Paeoniaceae family, has many intriguing actions, including being spasmolytic and possibly hormone modulating. Based on several studies in animal models of RA, it also likely has inflammation- and immune-modulating effects.[40] One randomized trial in 61 Chinese RA patients treated all with methotrexate, but half were simultaneously given a total glucoside extract of white peony at an unknown dose.[41] After three months, more of the patients

in the combination group than the methotrexate-only group had achieved a clinically effective result, though the difference was not significant. White peony extract was very safe, though it showed little basis for adding it to treatment.

An open trial randomized 204 Chinese RA patients taking methotrexate and leflunomide and compared the effects of this same extract of white peony to no additional treatment.[42] These two immunosuppressive drugs, though potentially more active than either alone, are also both potentially hepatotoxic, a problem augmented by their combination.[43] After six months of treatment, hepatotoxicity was significantly less common in the white peony group compared to untreated controls. There was a nonsignificant improvement in RA symptoms in the white peony group compared to the drugs-only group as well. Many preclinical studies confirm that white peony is hepatoprotective.[44–46] For this reason alone, white peony should be considered for use in combination with these drugs, though more rigorous studies would be welcome to confirm whether it is effective.

A formula combining unknown ratios of *Clematis mandshurica* (clematis, wēi líng xiān) root, *Trichosanthes kirilowii* (trichosanthes, guā lóu pí) fruit, and *Prunella vulgaris* (heal-all) flowering tops was assessed in 183 Korean RA patients in a double-blind trial.[47] Participants were randomized to 200 mg of the formula t.i.d. or celecoxib 200 mg b.i.d. for six weeks and continued prior treatments (immunosuppressives or NSAIDs) during the trial. There was no difference between the treatment groups in terms of symptom relief, with about 33% of each group achieving at least a 20% reduction in symptoms by week 6. Use of rescue pain medication did not differ between the groups, and adverse effects were also not significantly different. This rigorous trial suggests this herbal formula is a safe alternative to celecoxib for pain relief in RA patients.

An open clinical trial randomized 180 Chinese RA patients with peptic ulcers due to prior therapy, all of whom were taking celecoxib, methotrexate, and esomeprazole, to one of three groups: (1) moxa applied over ginger applied over the acupuncture point stomach 36, (2) the herbal formula san huang wu ji plus the same acupuncture, or (3) no additional treatment.[48] San huang wu ji, a modern Chinese herbal formula, contained *Sepiella japonica* (cuttlefish bone, hǎi piāo xiāo) 33%, *Phellodendron amurense* (Amur cork tree, huáng bǎi) bark 16%, *Bletilla striata* (bletilla, bái jí) rhizome 16%, *Scutellaria baicalensis* (Chinese skullcap, huáng qín) root 15%, *Coptis chinensis* (goldthread, huáng lián) root 11%, and *Pheretima aspergillum* (earthworm, dì long) 9%. It was administered as an oral powder at a dose of 10 g t.i.d. Treatment was for eight weeks, and then repeat endoscopy was performed. Ulcer healing was significantly greater in the combination therapy group compared to either of the other two groups. RA symptom severity, erythrocyte sedimentation rate (ESR), C-reactive protein levels, and gastrointestinal symptoms all improved significantly better in the combination treatment group than either of the other two groups. This promising treatment protocol was very safe and could be considered for clinical use while additional trials are performed.

Tripterygium wilfordii

Tripterygium wilfordii (thunder duke vine, léi gong téng) root and stem without bark, often mistranslated as thunder god vine, is a potent immunosuppressive medicine in the Celastraceae family.[49] Traditionally, a simple decoction of the whole root was used, but this is associated with unacceptably high rates of serious adverse effects, including hepatotoxicity, sterility, diarrhea, and bone-marrow suppression.[50] This led to the development of two safer extracts of the root and stem with bark removed, one using ethanol and ethyl acetate as solvents and the other chloroform and methanol. Most modern studies of thunder duke vine for RA have used one of these two extracts. They are not readily available in North America and, given their still significant risk for serious adverse effects, are not recommended for general use until well-documented products with excellent quality control become available. If and when such extracts become available, they could be valuable, as discussed below. Diterpenoids, including triptolide, tripdiolide, and triptonide, which have an unusual epoxide bridge structure, have been identified as particularly important compounds for imparting the immunosuppressive qualities of this herbal medicine.[51]

A meta-analysis of 10 randomized clinical trials assessed the effect of these two extracts of thunder duke vine to placebo or immunosuppressive drugs for RA patients.[52] Two trials compared thunder duke vine extracts to placebo and eight to immunosuppressive drugs as controls. Four of the trials were judged to be of high quality, and the remainder low. Compared to placebo, swollen joint counts, duration of morning stiffness, grip strength, and ESR were significantly reduced by thunder duke vine extracts. There was little difference between effectiveness of immunosuppressive drugs compared to this herb, except for a significant improvement in grip strength in the thunder duke vine groups. Only one trial used the industry standard ACR symptom score improvement, a significant weakness in these trials, so results could not be pooled for this outcome. Adverse effects were generally limited to digestive upset, dysmenorrhea, amenorrhea, mild liver abnormalities, and mild prolongation of the QT interval. In the best quality study, which compared thunder duke vine to sulfasalazine in RA patients, there were 17 patients who discontinued the drug due to adverse effects compared to just eight for thunder duke vine. This provides moderate evidence that these thunder duke vine extracts are safer and just as effective as immunosuppressive drugs for RA patients.

A meta-analysis of six randomized clinical trials comparing methotrexate alone to methotrexate plus thunder duke vine extracts concluded such combination therapy was more effective with similar safety as methotrexate monotherapy.[53] A single trial in 46 Chinese RA patients found a combination of a glycoside extract of 10 mg t.i.d. of thunder duke vine and etanercept, a biologic drug that blocks tumor necrosis factor alpha, to be as effective as etanercept and methotrexate, with no difference in the low rates of adverse effects between the treatments.[54] This is one of the only trials on any herb combined

with a biologic drug. More research is needed, but this is promising that this herb may be safely used with such agents.

One double-blind, randomized trial compared a topical preparation of thunder duke vine to placebo in 174 Chinese RA patients.[55] The compound was applied in a dose of 20 g once daily for eight weeks. Joint pain relief, visual analog pain scale, disease activity score in 28 joints (a standard measure of efficacy in RA trials), general health, ESR, and C-reactive protein levels were all significantly improved by the topical preparation compared to placebo. No menstrual problems occurred, and adverse effects were not different between the groups. More research is needed, but topical thunder duke vine may be a particularly safe way to deliver the medication without sacrificing efficacy.

Several herbs have been looked at as adjuncts to thunder duke vine extracts to lower toxicity and sometimes to enhance efficacy. *Glycyrrhiza uralensis* (gān cǎo, Chinese licorice) in an unknown dose was shown to both reduce toxicity and enhance efficacy of thunder duke vine decoction compared to thunder duke vine glycoside extract alone in a randomized trial.[56] As an immunomodulator and inflammation modulator itself, Chinese licorice is particularly well suited to patients with RA. Chinese licorice's key constituent glycyrrhetinic acid or its glycoside glycyrrhizin have been reported to speed clearance of thunder duke vine diterpenoids in preclinical models, both due to P-glycoprotein and CYP3A4 upregulation.[57,58] The antioxidant and other properties of Chinese licorice constituents are thought to also contribute to its protective effects against toxicity of thunder duke vine.[59] Though not confirmed in clinical trials like Chinese licorice has been, *Panax notoginseng* (sanqi ginseng) root and quercetin have also been shown to reduce thunder duke vine hepatotoxicity in rodents.[60,61]

Conclusion

Though much work remains to be done to identify optimal use of herbs in RA patients, there is at least preliminary evidence that some may be useful. In most cases, this is particularly true when they are used instead of immunosuppressive drugs, rather than added to them. However, patients should not discontinue their medications without consulting with knowledgeable healthcare providers about substituting herbs. The best studied herbs have been presented here to help guide practitioners to make choices about herbal therapies for patients. ■

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