



## Herbs and dietary supplements in rheumatoid arthritis: The clinical evidence

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### ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that results in the destruction of joint cartilage and bone with an accompanying cluster of inflammatory symptoms leading to the progressive deformity of multiple joints. Several disease modifying anti-rheumatic drugs (DMARDs) are available for the treatment of RA (which arrest or slow disease progression); however, these are sometimes associated with severe side effects. The market is inundated with herbal preparations and dietary supplements are as beneficial to relieve symptoms in RA either as alternatives to or for use alongside conventional medicines. This mini-review sought to determine whether these therapies are safe and efficacious for the treatment of RA. The strongest clinical evidence exists for short-term complementary use of *Tripterygium wilfordii* Hook F “thunder god vine”,  $\gamma$ -linolenic acid and fish oils for symptomatic relief. However, no long-term studies support the use of these supplements to either arrest or delay disease progression. Only a few studies are available for saffron, cinnamon, ginger and pomegranate which are insufficient to establish safety and efficacy. Other studies have shown that integrating traditional Chinese medicine with western medicine may be beneficial; however, most of these studies were poorly designed. A few studies have shown that folic acid and folinic acid supplementation may reduce the incidence of methotrexate-induced side effects and prevent discontinuation.

**Conclusion** There is limited and biased evidence regarding the efficacy of probiotics.

**Keywords:** rheumatoid arthritis, *Tripterygium wilfordii* Hook F, fish oils,  $\gamma$ -linolenic acid.



## 1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease with a worldwide prevalence of 0.46% [1]. It occurs with advancing age and has higher incidence in women. Susceptibility genes, smoking, family history of RA and being overweight are significant risk factors associated with RA [2].

In the early asymptomatic phase (which can last a few years) the autoimmune response leads to increased levels of circulating of pro-inflammatory mediators (cytokines and chemokines) and C-reactive protein (CRP). Consequently, immune cell infiltration occurs with accompanying progressive synovial hyperplasia and pannus formation [3]. The progressive accumulation of autoantibodies leads to cartilage and bone destruction. Morning stiffness, joint pain and tenderness, restriction in joint mobility and deformity in multiple joints over time are the classical clinical features of rheumatoid arthritis. The disease activity score in 28 joints (DAS28) is a scoring algorithm that monitors disease severity and the impact of therapy [4].

Although early and aggressive treatment may slow or even halt the progression of RA, drug therapy is associated with several adverse effects. Consequently, many people seek “natural” remedies.

## 2. DRUG TREATMENT FOR RHEUMATOID ARTHRITIS AND THEIR ASSOCIATED RISKS

Conventional treatments for RA include NSAIDs for pain relief, steroids as anti-inflammatory agents and disease modifying anti-rheumatic drugs (DMARDs) which arrest or slow disease progression. Conventional synthetic DMARDs include methotrexate (MTX), azathioprine, mycophenolate, leflunomide, cyclophosphamide, cyclosporine, hydroxychloroquine, sulfasalazine and tofacitinib (a targeted small synthetic molecule). Over the last decade the arsenal of drugs available has expanded to include biologic DMARDs which specifically target immune cells such as T-cells (abatacept) and B-cells (rituximab); as well as anti-IL-6 receptor antibody (tocilizumab), IL-1 inhibitors (anakinra) and TNF- $\alpha$  inhibitors (adalimumab, certolizumab, etanercept, golimumab and infliximab) [5].

DMARDs suppress the immune system and increase the risk of upper respiratory tract and urinary tract infections, increase the risk of skin cancers (TNF- $\alpha$  inhibitors), induce bone marrow suppression (azathioprine), thrombocytopenia (cyclosporine), gastrointestinal adverse effects (leflunomide, MTX, mycophenolate, sulfasalazine) and hepatotoxicity (MTX, azathioprine). Therefore, despite the proven efficacy of these drugs, the myriad of adverse effects pushes many patients to seek alternative “natural” remedies.

## 3. HERBAL MEDICINES IN RHEUMATOID ARTHRITIS

Several herbal preparations and dietary supplements are available in the market and are recommended for use in RA, but these are not regulated as stringently as conventional allopathic drugs [6]. Therefore, evidence for their use should come from



well-designed clinical trials, systematic reviews and meta-analyses that would provide robust evidence regarding their safety and efficacy. This mini-review examined the clinical evidence for herbal preparations and dietary supplements used in RA. Electronic searches were performed in the Cochrane Library Advanced Search (PubMed, Embase, CT.gov, ICTRP, & CINAHL), PubMed and EBSCOHOST databases from inception until April 2021. The search terms included rheumatoid arthritis, arthritis, herbal medicine, dietary supplement, traditional Chinese medicine, randomized clinical trial, systematic review and meta-analysis. Tables 1 and 2 summarize the clinical evidence for the use of herbs and dietary supplements in the treatment of rheumatoid arthritis.

### 3.1 *Tripterygium wilfordii* Hook F

Extracts of the roots of *Tripterygium wilfordii* Hook F (TwHF), known as “lei gong teng” or “thunder god vine”, have been used for centuries in traditional Chinese medicine (TCM) with use in the treatment of autoimmune and inflammatory conditions, including RA. Laboratory studies have identified diterpenoid compounds (triptolide, triptolide and triptonide) as the active ingredients responsible for the immunosuppressant and anti-inflammatory effects [7].

A systematic review conducted by Cameron and colleagues [8] included three placebo-controlled studies, with one comparing the extract to sulfasalazine. There were improvements in some outcomes; however, limited studies to pool a meta-analysis could not be performed to determine whether there were differences between the interventions and outcomes. Although one study reported serious side effects, long-term observations determined that these were mild to moderate in severity and resolved after discontinuation.

For decades *Tripterygium wilfordii* Hook F (TwHF) extracts has been combined with MTX for the treatment of RA in China. A systematic review and meta-analysis by Wang and colleagues

[9] included six trials with 643 patients which compared the effects of MTX alone and combined with *Tripterygium* glycosides. The reviewers found that the combination resulted in a 50% increase in responder rates with significant reductions in the number of swollen and tender joints. Additionally, there was shortened duration of morning stiffness, decreased ESR, CRP and rheumatoid factor levels. Regarding safety, the addition of TwHF did not increase the rate of adverse events. The reviewers concluded that combined MTX and TwHF therapy may be more effective and have a similar safety profile compared to MTX monotherapy. Larger trials are required to confirm these findings.

A more recent systematic review of 10 studies in 1,184 patients found that the use of *Tripterygium* extracts alone showed significantly better efficiency than MTX alone [10]. Furthermore, the combined use of *Tripterygium* extracts and MTX showed significantly better efficiency than MTX alone. Despite these positive findings the reviewers noted the overall poor methodological quality of included studies and recommended that



future trials should be better designed and sufficiently powered.

### 3.2 Saffron

Saffron is a spice that is thought to possess multiple medicinal properties. A clinical trial by Hamidi and colleagues included 66 women with active RA which compared the efficacy of daily consumption of a saffron supplement (100mg) with placebo over a 12-week period [11]. The researchers evaluated the effect of supplementation on clinical outcomes and metabolic profiles.

It was found that saffron supplementation significantly decreased the number of tender and swollen joints, pain intensity (based on visual analog scale - VAS), Disease activity score (DAS28) and Physician Global Assessment. There was a significant improvement in ESR, as well as reductions in high-sensitivity CRP, TNF- $\alpha$ , IF- $\gamma$  and malondialdehyde. However, total antioxidant capacity was not significantly changed. The researchers concluded that supplementation with saffron supplements positively and significantly improve clinical outcomes in RA.

### 3.3 Cinnamon

Cinnamon is a commonly used spice and also reported to be useful in the management of symptoms of RA. Shishehbor and colleagues conducted a randomized control trial in 36 women with RA which compared the daily consumption of 500mg cinnamon powder with placebo over an 8-week period [12]. The researchers evaluated the effect of cinnamon supplementation on disease activity, serum levels of inflammatory markers and cardiovascular risk factors. Serum levels of CRP, TNF- $\alpha$ , erythrocyte sedimentation rate (ESR) and clinical symptoms of RA were also measured at baseline and at week 8.

The researchers found that cinnamon supplementation produced a significant decrease in both CRP and TNF- $\alpha$ , as well as a significant reduction in Disease Activity Score (DAS-28), VAS and the number of tender and swollen joints. It was noted that there were no significant changes in liver enzymes or ESR. It was concluded that cinnamon may be a safe and potential adjunct treatment to improve inflammation and clinical symptoms in patients with RA.

### 3.4 Ginger

Ginger is another commonly used food additive and spice that has been recommended to relieve symptoms in RA. A clinical trial conducted by Aryaeian and colleagues included 70 patients with active RA which sought to determine the efficacy of daily consumption of ginger powder (1500mg) over 12 weeks compare with placebo [13]. The researchers investigated the effect of ginger supplementation on the expression of a few immunity and inflammation intermediate genes in RA patients.

It was found that supplementation produced statistically significant effects on the expression of immunity and inflammation intermediate factors, as well as reduced



disease activity score compared with placebo. They concluded that ginger may improve RA severity by modulating gene expression of inflammatory markers.

### 3.5 Pomegranate

Pomegranate juice is rich in polyphenolic compounds known to possess antioxidant and anti-inflammatory activities. An 8-week randomized controlled trial in RA patients sought to determine whether daily consumption of 250mg pomegranate extract (POMx) was more efficacious than placebo (cellulose, 250mg) to relieve symptoms [14].

The researchers collected data at baseline and the end of the study using the Health Assessment Questionnaire (HAQ) and Disease Activity Score (DAS28), as well as laboratory markers for inflammation and oxidative stress to include CRP, matrix metalloproteinases 3 (MMP3), malondialdehyde (MDA), glutathione peroxidase (GPx) and erythrocyte sedimentation rate (ESR).

It was found that POMx significantly reduced DAS28 score which could be related to decrease in the number of swollen and tender joints, pain intensity and ESR levels. Consumption of the extract also decreased HAQ score, morning stiffness and increased GPx concentrations. There were no differences between treatment groups for MMP3, CRP and MDA. It was concluded that POMx alleviates disease activity and improves some biomarkers of inflammation and oxidative stress in RA patients.

### 3.6 Integrated Traditional Chinese Medicine and Western Medicine

Traditional Chinese Medicine (TCM) is a centuries-old medical tradition and has been integrated with western medicine or allopathic medicine (WM) in many Asian countries in the treatment of many diseases, including RA. A systemic review by Zing and colleagues assessed 20 clinical trials (with 2269 patients) which compared the efficacy and safety of integrated TCM-WM with WM alone in the treatment of RA [15].

This review found significant improvements in the integrated approach compared with WM alone for multiple comparators. There were significant improvements in therapeutic effects with reductions in the number of tender and swollen joints, morning stiffness and DAS28 score. There were also significant reductions in inflammatory markers, including rheumatoid factor, ESR and CRP.

There were significant reductions in adverse events associated with conventional drugs, such as gastrointestinal disorders, abnormal liver function, leukopenia, skin allergies, rashes, headaches, dizziness and alopecia in TCM-WM group. The reviewers concluded that integrative TCM-WM could obtain effective and safe results in RA and that using TCM as an adjunctive therapy in RA has promising prospects for further research.

### 3.7 Other herbal medicines

Several other herbal medicines are recommended for use in the treatment of RA, including *Boswellia* spp. (frankincense), *Curcuma longa* (turmeric), *Eremostachys laciniata*, *Eucommia ulmoides*, *Matricaria chamomilla* (chamomile), *Paeonia lactiflora* and *Withania somnifera* (Ashwagandha). However, there is very limited clinical evidence to support their use.

Table 1. Summary of clinical evidence of herbs and dietary supplements in rheumatoid arthritis

Herbal medicine	No. of randomized clinical trials	Systematic review	Beneficial effects
TwHF alone	3	Yes	+
TwHF alone + MTX	6; 10	Yes	+++
Saffron	1	No	+
Cinnamon	1	No	+
Ginger	1	No	+
Pomegranate	1	No	+
TCM + Western (Allopathic) Medicine	20	Yes	+++

## 4. DIETARY SUPPLEMENTS IN RHEUMATOID ARTHRITIS

### 4.1 Fish Oils

It is thought that omega-3 fatty acids, abundant in fatty fish, interrupt the biological pathway which produces important pro-inflammatory molecules in RA [16]. A systematic review by Senftleber and colleagues evaluated 42 randomized controlled clinical trials (in 2571 RA patients) to determine whether marine oil supplements reduced pain and/or improved other clinical outcomes in these patients [17]. The review included 22 trials in patients with RA and found a significant effect in pain reduction. Subsequently, the reviewers concluded that the evidence for the use of marine oil to alleviate pain in arthritis patients of moderate quality in RA.

### 4.2 Gamma-linolenic acid (GLA)

Gamma-linolenic acid (GLA), found in the essential oils in the seeds of evening primrose, borage and blackcurrant, has emerged as an alternative remedy in the treatment of RA. GLA provides an alternative to arachidonic acid leading to less inflammatory or anti-inflammatory compounds which directly block the production of



natural pro-inflammatory compounds [18].

A systematic review by Cameron and colleagues included seven clinical trials which found that GLA supplementation produced significant reductions in pain intensity and improved mobility [8]. However, there was an increase in the incidence of adverse events, although this was not statistically significant. The reviewers concluded that there is moderate evidence that GLA may relieve symptoms in RA.

#### 4.3 Vitamin D

Observational studies have shown that the higher incidence of autoimmune diseases in temperate countries may be linked to vitamin D deficiency [19]. Laboratory in vitro studies have shown wide-ranging effects of Vitamin D on the immune system (immune cells, cytokines).

These effects include decreases in IL-2 and IF- $\gamma$  (Th1 response), increases in IL-4 (Th2 response), stimulatory effects on regulatory T cells and inhibitory effects on Th17 and Th9 lymphocytes [20].

However, a systematic review in five clinical studies shows that Vitamin D supplementation had no statistical significant effect on pain (using VAS) or disease activity score (DAS28) [21]. However, there was a non-significant decrease in recurrence and it was concluded that although Vitamin D supplementation may reduce RA recurrence, more robust trials were needed to confirm these findings.

#### 4.4 Probiotics

Probiotics are considered immunomodulatory [22]; however, their efficacy as adjunct therapy in RA is controversial. A systematic review by Rudbane and colleagues included four clinical trials (in 153 patients; 89% female) which showed that probiotics (compared to placebo) had no significant effect to alter mediators of inflammation (ESR, TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-10, and IL-12) or indices of oxidative stress (total antioxidant capacity and malondialdehyde) [23]. However, there was a borderline significant reduction in CRP. However, disease activity score [DAS28] and the number of tender and swollen joints showed significant improvement. The reviewers concluded that the number of trials was too small to determine whether a strain-, dose-, or duration-response effect was present.

#### 4.5 Folic acid to reduce methotrexate-induced side effects

MTX antagonizes folic acid metabolism with several side effects (mucosal, gastrointestinal, hepatic and haematological). It is postulated that these side effects could be alleviated by supplementation with folic or folic acid. A systematic review of six trials (with 624 patients) evaluated the effect of folate (starting at  $\leq 7$  mg/week) in adult RA patients treated with MTX ( $\leq 25$  mg/week) [24].

The reviewers found that supplementation produced a 26% relative (9% absolute)





reduction in the incidence of MTX-induced gastrointestinal side effects. Folate supplementation was protective against MTX-induced serum transaminase elevation, with 77% relative (16% absolute) and reduced the MTX withdrawal rate for any reason by 61% (15% absolute). However, supplementation had no significant effect on the efficacy of MTX, i.e. on disease activity (number of tender and swollen joints) or physician's global assessment scores.

It was concluded that the protective effect of folate supplementation in RA patients treated with MTX included significant reductions in incidence of gastrointestinal side effects, hepatic dysfunction, as well as a significant reduction in discontinuation of MTX treatment for any reason.

Table 2. Summary of clinical evidence of dietary supplements in rheumatoid arthritis

Dietary supplement	No. of randomized clinical trials	Systematic review	Beneficial effects
Fish Oils	22	Yes	+++
Gamma-linoleic acid (GLA)	7	Yes	+++
Vitamin D	5	Yes	-/+
Probiotics	4	Yes	-/+
Folinic acid – for reduction in MTX-induced side effects	6	Yes	++

## CONCLUSION

With the ready access to herbal preparations and dietary supplements for the treatment of RA the strongest evidence exists for short-term complementary use of *Tripterygium wilfordii* Hook F,  $\gamma$ -linolenic acid and fish oils for symptom relief and improvement in quality-of-life.

However, there are no long-term studies that would support the use of these supplements to either arrest or delay disease progression. With only single studies for saffron, cinnamon, ginger and pomegranate the evidence is insufficient to establish efficacy of these herbs. A few studies have shown that folic acid and folinic acid supplementation may be useful to reduce MTX-associated side effects and prevent discontinuation. There is very limited and biased evidence regarding the utility of probiotics.





## REFERENCES

- 1 Almutairi K, Nossent J, Preen D, Keen H, Inderjeeth C. The global prevalence of rheumatoid arthritis: a meta-analysis based on a systematic review. *Rheumatology International*. 2021; 41: 863–77.
- 2 Centers for Disease Control and Prevention. Risk Factors: Factors that increase risk of getting arthritis. <https://www.cdc.gov/arthritis/basics/risk-factors.htm> [Accessed 24 June 2021].
- 3 Demoruelle MK, Deane KD, Holers VM. When and Where Does Inflammation Begin in Rheumatoid Arthritis? *Curr Opin Rheumatol*. 2014; 26(1): 64–71. doi: 10.1097/BOR.0000000000000017
- 4 Porter D, Gadsby K, Thompson P, White J, McClinton C, Oliver S. DAS28 and Rheumatoid Arthritis: The Need for Standardization. *Musculoskeletal Care*. 2011; 9(4): 222–7. doi: 10.1002/msc.218.
- 5 Negm AA, Furst DF. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics, and drug used in gout. In: Katzung BG (ed). *Basic and Clinical Pharmacology*, 14th edition. New York: McGraw-Hill Education. 2018. p. 642–66.
- 6 Natural Remedies for Rheumatoid Arthritis Pain Relief. WebMD. <https://www.webmd.com/rheumatoid-arthritis/rheumatoid-arthritis-natural-treatments>. [Accessed 24 June 2021].
- 7 Lv H, Jiang L, Zhu M, Li Y, Luo M, Jiang P, et al. The genus *Tripterygium*: A phytochemistry and pharmacological review. *Fitoterapia*. 2019; 137: 104190. doi: 10.1016/j.fitote.2019.104190.
- 8 Cameron M, Gagnier JJ, Chrubasik S. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database Syst Rev*. 2011; (2):CD002948. doi: 10.1002/14651858.CD002948.pub2.
- 9 Wang X, Zu Y, Huang L, Yu J, Zhao H, Wen C, et al. Treatment of rheumatoid arthritis with combination of methotrexate and *Tripterygium wilfordii*: A meta-analysis. *Life Sci*. 2017; 171: 45–50. doi: 10.1016/j.lfs.2017.01.004.10
10. Chen WJ, Li TX, Wang XY, Xue ZP, Lyu C, Li HZ, et al. [Meta-analysis of RCT



studies on clinical efficacy of single administration of Tripterygium Glycosides Tablets or combined administration with methotrexate against rheumatoid arthritis]. *Zhongguo Zhong Yao Za Zhi.* 2020; 45(4): 791-797. doi: 10.19540/j.cnki.cjcmm.20191115.503.

11 Hamidi Z, Aryaeian N, Abolghasemi J, Shirani F, Hadidi M, Fallah S, et al. The effect of saffron supplement on clinical outcomes and metabolic profiles in patients with active rheumatoid arthritis: A randomized, double-blind, placebo-controlled clinical trial. *Phytother Res.* 2020; 34(7): 1650-1658. doi: 10.1002/ptr.6633.

12 Shishehbor F, Safar MR, Rajaei E, Haghighizadeh MH. Cinnamon Consumption Improves Clinical Symptoms and Inflammatory Markers in Women with Rheumatoid Arthritis. *J Am Coll Nutr.* 2018;1-6. doi: 10.1080/07315724.2018.1460733.

13 Aryaeian N, Shahram F, Mahmoudi M, Tavakoli H, Yousefi B, Arablou T, et al. The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis. *Gene.* 2019; 698: 179-185. doi: 10.1016/j.gene.2019.01.048.

14 Ghavipour M, Sotoudeh G, Tavakoli E, Mowla K, Hasanzadeh J, Mazloom Z. Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in Rheumatoid Arthritis patients. *Eur J Clin Nutr.* 2017; 71(1): 92-96. doi: 10.1038/ejcn.2016.151.

15 Xing Q, Fu L, Yu Z, Zhou X. Efficacy and Safety of Integrated Traditional Chinese Medicine and Western Medicine on the Treatment of Rheumatoid Arthritis: A Meta-Analysis. *Evid Based Complement Alternat Med.* 2020; 2020: 4348709. doi: 10.1155/2020/4348709.

16 Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. *Biochim Biophys Acta.* 2015;1851(4):469-84. doi: 10.1016/j.bbali.2014.08.010.

17 Senftleber NK, Nielsen SM, Andersen JR, Bliddal H, Tarp S, Lauritzen L, et al. Marine Oil Supplements for Arthritis Pain: A Systematic Review and Meta-Analysis of Randomized Trials. *Nutrients.* 2017; 9(1): 42. doi: 10.3390/nu9010042.

18 Kapoor R, Huang YS. Gamma linolenic acid: an antiinflammatory omega-6 fatty acid. *Curr Pharm Biotechnol.* 2006; 7(6): 531-4. doi: 10.2174/138920106779116874.

19 Harrison SR, Li D, Jeffery LE, Raza K, Hewison M. Vitamin D, Autoimmune Disease and Rheumatoid Arthritis. *Calcif Tissue Int.* 2020; 106(1): 58-75. doi: 10.1007/s00223-019-00577-2.

20 Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. *Nutrients.* 2013; 5(7): 2502-21. doi: 10.3390/nu5072502.

21 Silva Franco A, Quadrante Freitas T, Bernardo WM, Pereira RMR. Vitamin D



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supplementation and disease activity in patients with immune-mediated rheumatic diseases: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2017; 96(23): e7024. doi: 10.1097/MD.00000000000007024

22 Maldonado Galdeano C, Cazorla SI, Lemme Dumit JM, Vélez E, Perdigón G. Beneficial Effects of Probiotic Consumption on the Immune System. *Ann Nutr Metab*. 2019; 74(2): 115-124. doi: 10.1159/000496426.

23 Rudbane SMA, Rahmdel S, Abdollahzadeh SM, Zare M, Bazrafshan A, Mazloomi SM. The efficacy of probiotic supplementation in rheumatoid arthritis: a meta-analysis of randomized, controlled trials. *Inflammopharmacology*. 2018; 26(1): 67-76. doi: 10.1007/s10787-017-0436-y.

24 Shea B, Swinden MV, Tanjong Ghogomu E, Ortiz Z, Katchamart W, Rader T, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. *Cochrane Database Syst Rev*. 2013; 2013(5): CD000951. doi: 10.1002/14651858.CD000951.pub2.