

MEDICINAL PLANTS IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS: A REVIEW OF THERAPEUTIC POTENTIAL

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RESUME

Rheumatoid arthritis is an immunologic disease that causes significant systemic effects, shortens life, and reduces mobility and quality of life. Interest has centered on finding treatments that might arrest—or at least slow—this progression by modifying the disease itself. The effects of disease-modifying therapies may take 6 weeks to 6 months to become clinically evident, although some biologics are effective within 2 weeks or less.

Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people. Adverse effects and complications of analgesic drugs, such as addiction, kidney failure, and gastrointestinal bleeding, also limit their use. Herbal medicine offers a multimodality treatment approach that can tackle the multidimensional nature of pain with fewer or no serious adverse effects. This review summarizes clinical studies conducted by different scientists on the efficacy of commonly used medicinal plants in the treatment of rheumatoid arthritis, such as **Borago officinalis**, **Nigella sativa** (blackcurrant seed oil), **Oenothera biennis** (evening primrose oil), **Curcuma** (turmeric), **Salix alba** (willow bark), **Tripterygium Wilfordii** Hook, **Harpagophytum procumbens**, **Capsicum**, and **Rosa canina** (rosehip).

In accordance with the conducted researches, no strong evidence shows that herbal medicine reduces pain in rheumatoid arthritis. However, borage seed oil and curcumin/turmeric have slightly more evidence and may be tried in treatment of resistant rheumatoid arthritis.

Some herbs and herbal mixtures from traditional Chinese and Ayurvedic medicine might be beneficial in rheumatoid arthritis, but their safety is not yet proven. Further traditional therapies and whole medical systems may effectively contribute to pain management in rheumatoid arthritis, although the evidence is still preliminary. Taken together, medicinal herbs have an increasing role in the management of chronic pain, but high quality research is needed.

Key Words: Rheumatoid arthritis, **Borago officinalis**, **Nigella sativa** (blackcurrant seed oil), **Oenothera biennis** (evening primrose oil), **Curcuma** (turmeric), **Salix alba** (willow bark), **Tripterygium Wilfordii** Hook, **Harpagophytum procumbens**, **Capsicum**, and **Rosa canina** (rosehip).

სამკურნალო მცენარეები რევმატოიდული ართრიტის მართვაში: თერაპიული პოტენციალის მიმოხილვა

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რეზიუმე

რევმატოიდული ართრიტი წარმოადგენს ქრონიკულ, სისტემურ, აუტოიმუნურ დაავადებას, რომელიც ასოცირდება მნიშვნელოვანი ორგანოსისტემური დაზიანებით, პაციენტთა სიცოცხლის ხანგრძლივობის შემცირებით, ფუნქციური შესაძლებლობების შეზღუდვით და ცხოვრების ხარისხის მნიშვნელოვანი დაქვეითებით. ბოლო ათწლეულებში სამეცნიერო კვლევები ინტენსიურად მიმართულია ისეთი თერაპიული სტრატეგიების განვითარებისკენ, რომლებიც მიზნად ისახავს დაავადების მიმდინარეობის შეცვლას (Disease-Modifying Therapies, DMTs) და პათოფიზიოლოგიური პროცესების პროგრესირების შეჩერებას. დაავადების მოდიფიკაციის თერაპიების კლინიკური ეფექტის გამოვლინებას, როგორც წესი, სჭირდება 6 კვირიდან 6 თვემდე პერიოდი, თუმცა გარკვეული ბიოლოგიური აგენტები სწრაფი თერაპიული ეფექტურობით ხასიათდებიან და კლინიკური პასუხი შესაძლებელია დაფიქსირდეს 2 კვირის ვადაში ან უფრო მალე.

მიუხედავად ქრონიკული ტკივილის მართვის სფეროში მიღწეული პროგრესისა, ტკივილის ადეკვატური კონტროლი მნიშვნელოვან გამოწვევად რჩება. ტკივილგამაყუჩებელი საშუალებების ხანგრძლივი გამოყენება ასოცირდება რიგ გართულებებთან, როგორიცაა ოპიოიდური დამოკიდებულება, თირკმლის ფუნქციის გაუარესება და კუჭ-ნაწლავის სისტემის სისხლდენითი გართულებები, რაც ზღუდავს მათი გამოყენების უსაფრთხოებას და ეფექტურობას გრძელვადიან პერსპექტივაში. მოცემულ კონტექსტში მცენარეული მედიცინა განიხილება როგორც მულტიმოდალური თერაპიული მიდგომა, რომელიც მიზნად ისახავს ტკივილის მრავალგანზომილებიანი ბუნების მართვას, პოტენციურად ნაკლები და შედარებით მსუბუქი გვერდითი

მოვლენებით. მოცემული მიმოხილვა სინთეზურად აჯამებს კლინიკური კვლევების მონაცემებს მცენარეულ პრეპარატებზე, რომლებიც ფართოდ გამოიყენება ქრონიკული ტკივილის სამკურნალოდ, და აანალიზებს მათ ეფექტურობასა და უსაფრთხოების პროფილს არსებული სამეცნიერო მტკიცებულებების საფუძველზე. ეს მცენარეული პრეპარატებია **Borago officinalis**, **Nigella sativa** (blackcurrant seed oil), **Oenothera biennis** (evening primrose oil), **Curcuma** (turmeric), **Salix alba** (willow bark), **Tripterygium Wilfordii** Hook, **Harpagophytum procumbens**, **Capsicum**, and **Rosa canina** (rosehip). არსებული კვლევების შესაბამისად, მყარი მტკიცებულება იმის შესახებ, რომ სამკურნალო მცენარეები ეფექტურად ამცირებს რევმატოიდული ართრიტით გამოწვეულ ტკივილს, ამ ეტაპზე არ იკვეთება. თუმცა, **Borago officinalis**-ის თესლის ზეთსა და კურკუმას (**Curcuma longa**) ოდნავ მეტი მტკიცებულებითი მხარდაჭერა გააჩნია და მათი გამოყენება შესაძლებელია რეზისტენტული რევმატოიდული ართრიტის თერაპიაში.

ასევე, ტრადიციული ჩინური და აიურვედული მედიცინის მცენარეული პრეპარატები და ნარეგები შეიძლება სასარგებლო აღმოჩნდნენ რევმატოიდული ართრიტის მართვაში, თუმცა მათი უსაფრთხოების პროფილი ამ დროისთვის ჯერ კიდევ დაუდასტურებელია.

დამატებით, ტრადიციულ თერაპიულ მიდგომებსა და მთლიან სამედიცინო სისტემებს შესაძლოა ეფექტური როლი ჰქონდეთ რევმატოიდული ართრიტის ტკივილის მართვაში, თუმცა არსებული მტკიცებულებები კვლავ სანყის ეტაპზეა.

ჯამურად, სამკურნალო მცენარეების როლი ქრონიკული ტკივილის მართვაში მზარდია, თუმცა საჭიროა მაღალი ხარისხის კვლევების ჩატარება აღნიშნული მიმართულების სამეცნიერო დასაბუთებისთვის.

საკვანძო სიტყვები: **რევმატოიდული ართრიტი**, **Borago officinalis**, **Nigella sativa** (blackcurrant seed oil) and **Oenothera biennis** (evening primrose oil), **Curcuma** (turmeric), **Salix alba** (willow bark), **Tripterygium Wilfordii** Hook, **Harpagophytum procumbens**, **Capsicum**, and **Rosa canina** (rosehip).

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Rheumatoid arthritis is an immunologic disease that causes significant systemic effects, shortens life, and reduces mobility and quality of life. Interest has centered on finding treatments that might arrest—or at least slow—this progression by modifying the disease itself. The effects of disease-modifying therapies may take 6 weeks to 6 months to become clinically evident, although some biologics are effective within 2 weeks or less (1)

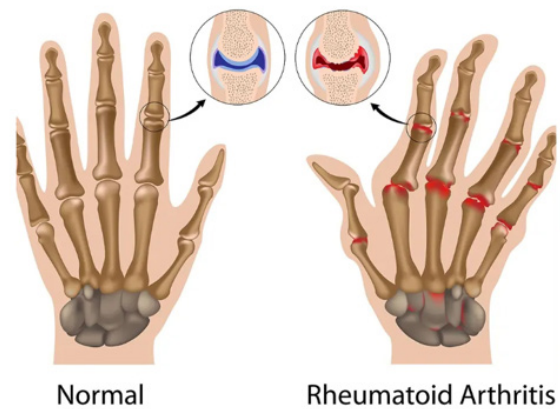


Figure 1. Rheumatoid arthritis

Complementary and integrative medicine (CIM) encompasses both Western-style medicine and complementary health approaches as a new combined approach to treat a variety of clinical conditions. Although advances have been made in treatments for chronic pain, it remains inadequately controlled for many people. Adverse effects and complications of analgesic drugs, such as addiction, kidney failure, and gastrointestinal bleeding, also limit their use. Herbal medicine offers a multimodality treatment approach that can tackle the multidimensional nature of pain with fewer or no serious adverse effects.

Despite their longstanding use, clinical evidence for herbal medicine and nutrients used in **rheumatoid arthritis** only limited data from high quality trials on the use of herbal medicine and specific plant based nutrients in rheumatic pain conditions are available (13).

Borago officinalis (borage seed oil) containing γ -linolenic acid (GLA) has been tested in two small placebo controlled RCTs over six months.

One included 37 patients with rheumatoid arthritis using 1.4 g GLA, and the other included 65 patients using 2.8g GLA daily from borage seed oil (2,3). Both studies found significant improvements in clinical pa-



Picture 2. *Borago officinalis*



Picture 2. *Borago officinalis*

parameters of rheumatoid arthritis including pain intensity ($P < 0.001$ each) after six months.

Nigella sativa (blackcurrant seed oil) and ***Oenothera biennis*** (evening primrose oil) are further rich sources of GLA.



Picture 3. *Nigella sativa* (blackcurrant seed)



Trials on these GLA sources used smaller daily doses (< 1.4 g/day) of GLA or did not report outcomes for pain.¹⁹⁴ Overall effects on rheumatoid arthritis were inconsistent, and rates of withdrawal were high owing to the number of large capsules needed for intake. A systematic review on herbal medicine in people with RA, comparing higher dose GLA (≥ 1.4 g daily) with placebo (including the two studies on borage seed oil), found significant improvements in pain (VAS) compared with placebo (mean difference -32.8 , -56.2 to -9.4) and a non-significant increase in adverse events (4).



Picture 4. *Oenothera biennis* (evening primrose)

Curcuma (turmeric) has shown profound anti-inflammatory effects in preclinical studies, with curcumin being the leading substance. The effectiveness of curcumin (500 mg twice daily) was compared with diclofenac (50 mg twice daily) or combination therapy in a small pilot clinical trial in 45 patients with rheumatoid arthritis. No differences were reported between the groups after eight weeks (15). A recent meta-analysis on turmeric extracts including three studies reporting pain in arthritis concluded that eight to 12 weeks of treatment with standardized turmeric extracts can reduce pain due to arthritis compared with placebo (VAS SMD -2.04 , -2.85 to -1.24). Adverse events were not increased with turmeric (7).



Picture 5. Curcuma (turmeric)

There are positive results for curcumin from turmeric, especially in high dose or enhanced bioavailability preparations. The efficacy of some of the above together has been established in a double blind controlled clinical trial and evidence for similar combinations exists elsewhere (12). *Zanthoxylum* (prickly ash) might be added in cases where cold and poor circulation are identified as factors.

Salix alba (willow bark) extract has been used for thousands of years as an anti-inflammatory and analgesic remedy. *Salix alba* is mostly used in standardized preparations containing 120 or 240 mg salicin. Only one small randomized study has compared 240 mg salicin daily with placebo in 26 patients with rheumatoid arthritis. There was no difference in pain after six weeks (8).



Picture 6. Salix alba (willow bark)

Tripterygium Wilfordii Hook F *Tripterygium Wilfordii* Hook F (**TWH; thunder god vine**) is traditionally used in China for the treatment of a broad spectrum of autoimmune and inflammatory diseases such as rheumatoid arthritis and ankylosing spondylitis.



Picture 7. Tripterygium Wilfordii Hook

In preclinical studies, triptolides were the major components accounting for the anti-inflammatory effect. An RCT including 121 patients with rheumatoid arthritis compared 2 g of sulfasalazine with 180 mg of a specific TWH extract. Outcomes were available for only 62 patients after 24 weeks. TWH was superior to sulfasalazine in terms of American College of Rheumatology (ACR) 20% clinical response (65% v 32.8%; $P=0.001$) and pain relief (mean differences not given) (5). Adverse events were more frequent with sulfasalazine. A further three armed RCT compared methotrexate (12.5 mg/week orally) with TWH (60 mg daily) and the combination of TWH and methotrexate in a multicenter trial of more than 200 rheumatoid arthritis patients. A 50% clinical response after 24 weeks was achieved in 46% with methotrexate, 55% with TWH, and 77% with the combination therapy ($P=0.0014$ for non-inferiority) (6). Adverse events were balanced between groups, with the exception of more irregular menstruation with TWH. A recent meta-analysis that included all available studies on TWH concluded that TWH could be as effective as synthetic DMARDs in the treatment of rheumatoid arthritis (7). However, the efficacy of TWH has to be confirmed with better designed RCTs. Furthermore, there is major concern about the safety of TWH. (8). The herb has a profound toxic potential if not extracted properly. Studies outside the field of rheumatic disease have noted an adverse effect on male fertility in both animals and humans and dysmenorrhea and amenorrhea in women.

A Cochrane review of clinical trials for low back pain, usually with arthritic elements, found that there was positive evidence for **Harpagophytum procumbens** (devil's claw), **Salix alba** and **Capsicum spp.** although there were methodological shortcomings in each case (9).



Picture 8. *Harpagophytum procumbens*

Many of the studies undertaken to examine the anti-inflammatory effects of devil's claw have demonstrated limited activity in standard inflammatory mod-

els. The anti-inflammatory effect varies with the route of administration and nature of the condition (acute or subacute).

Injection of devil's claw extract and harpagoside exhibited dose-dependent peripheral analgesic effects comparable to aspirin. (16). This activity was abolished by acid pretreatment of the herbal extract. In earlier work, intraperitoneal administration of harpagoside (20 mg/kg) produced an analgesic effect comparable to phenylbutazone (50 mg/kg) (17). However, harpagoside hydrolysed by emulsion (which would produce harpagogenin) was inactive. (17) No consistent analgesic effects were found in mice after oral doses of devil's claw extracts (18). In a later study, oral pretreatment with devil's claw extract (30 to 300 mg/kg, standardised to contain 1.9% harpagoside) did produce significant analgesic effects in the formalin test of mice. Naloxone (5 mg/kg, sc) significantly attenuated the analgesic effect of devil's claw, suggesting that the opioidergic system may be involved. (19). Devil's claw extract has also demonstrated analgesic activity against heat- and chemical induced pain in mice (50 to 800 mg/kg, 64:1 extract, ip injection) (20). and against heat-induced pain in rats (extract administered orally) (21).

A more recent contender for an arthritic treatment has been standardised preparations of **Rosa canina** (**rosehip**). In one double blind, controlled study among 100 patients with OA of the knee or hip, a modest benefit over placebo was detected over 4 months (10). In another double blind, placebo controlled crossover trial in 94 patients with the same condition, researchers found that the effect was minimal, but included some reduction of stiffness and symptoms, and reduced use of back-up analgesics (11).

Aqueous alcoholic or oily preparations of the fruits of various species of *Capsicum* are traditional topical remedies for arthritis, rheumatic complaints, and various kinds of pain, particularly when used in the form of alcohol extracts. The key active constituents are the capsaicinoids, especially capsaicin, whose content in the various species ranges from 0 to about 1.5%. When applied topically, capsaicin preparations incite an initial response consisting of erythema, pain, and warmth. This is followed by an extended period of insensitivity marked by a reversible desensitization of afferent nerve fibers. While the erythema, pain, and warmth subside within a few hours, the antinociceptive effects can persist for a period of hours to weeks. With repeated use, the vascular and sensory responses to the agent decline and are eventually extinguished (22).

Based on the information available at the time, the 1990 Commission E monograph on capsicum (paprika) stated that semisolid preparations (0.05-0.05 % capsaicinoids), liquid preparations (0.005-0.01 % capsaici-



Picture 9. *Capsicum* spp



Picture 10. *Rosa canina* (rosehip)

noids), and plasters were indicated for painful muscle spasm involving the shoulder, arm, or spinal region in adolescents and school age children. Since 1990 a number of controlled clinical studies have been published on the use of topical capsaicin-containing preparations for neuralgia and rheumatic complaints. These studies were based on treatment period ranging from 2 to 8 weeks. A 0.075% capsaicin cream was used in most of the studies. Capsaicin appeared to be superior to placebo. There were no side effects serious enough to warrant discontinuation of treatment, but there were occasional reports of a burning or pricking sensation. These complaints persisted for about 2 weeks and then resolved without sequelae (23).

Rosa canina (rose hip) contains a high amount of vitamin C and galactolipids, which are claimed to have anti-inflammatory properties. In a placebo controlled RCT in 89 patients with rheumatoid arthritis, intake of 5 g standardized rose hip extract significantly improved quality of life ($P=0.032$) and disease activity (DSA28; $P=0.056$) but not pain intensity. Between group differences were not reported(14).

CONCLUSION

In accordance with the conducted researches, no strong evidence shows that herbal medicine reduces pain in rheumatoid arthritis. However, borage seed oil and curcumin/turmeric have slightly more evidence and may be tried in treatment of resistant rheumatoid arthritis.

Some herbs and herbal mixtures from traditional Chinese and Ayurvedic medicine might be beneficial in rheumatoid arthritis, but their safety is not yet proven. Further traditional therapies and whole medical systems may effectively contribute to pain management in rheumatoid arthritis and back and neck pain, although the evidence is still preliminary. Taken together, medicinal herbs have an increasing role in the management of chronic pain, but high quality research is needed.

REFERENCES

1. Katzung, B.G, Masters, S.B., Trevor, A.J. Basic and Clinical Pharmacology. 12th edition. The McGraw-Hill Companies, Inc. 2012; p.643.
2. Leventhal LJ, Boyce EG, Zurier RB. Treatment of rheumatoid arthritis with gamma-linolenic acid. *Ann Intern Med* 1993;119:867-73. doi:10.7326/0003-4819-119-9-199311010-00001 pmid:8214997.
3. Zurier RB, Rossetti RG, Jacobson EW, et al. gamma-Linolenic acid treatment of rheumatoid arthritis. A randomized, placebo- controlled trial. *Arthritis Rheum* 1996;39:1808-17. doi:10.1002/art.1780391106 pmid:8912502.

4. Cameron M, Gagnier JJ, Chrubasik S. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2011;2:CD002948.p mid:21328257.
5. Goldbach-Mansky R, Wilson M, Fleischmann R, et al. Comparison of *Tripterygium wilfordii* Hook F versus sulfasalazine in the treatment of rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2009;151:229- 40, W49-51. doi:10.7326/0003-4819-151-4-200908180- 00005 pmid:19687490.
6. Lv QW, Zhang W, Shi Q, et al. Comparison of *Tripterygium wilfordii* Hook F with methotrexate in the treatment of active rheumatoid arthritis (TRIFRA): a randomised, controlled clinical trial. *Ann Rheum Dis* 2015;74:1078-86. doi:10.1136/annrheumdis-2013-204807 pmid:24733191.
7. Daily JW, Yang M, Park S. Efficacy of turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta- analysis of randomized clinical trials. *J Med Food* 2016;19:717-29. doi:10.1089/jmf.2016.3705 pmid:27533649.
8. Biegert C, Wagner I, Lüdtke R, et al. Efficacy and safety of willow bark extract in the treatment of osteoarthritis and rheumatoid arthritis: results of 2 randomized double-blind controlled trials. *J Rheumatol* 2004;31:2121-30.pmid:15517622.
9. Gagnier JJ, van Tulder M, Berman B, Bombardier C. Herbal medicine for low back pain. *Cochrane Database Syst Rev*.2006;(2):CD004504.
10. Warholm O, Skaar S, Hedman E, et al. The effects of a standardized herbal remedy made from a subtype of *Rosa canina* in patients with osteoarthritis: a double blind,randomized, placebo-controlled clinical trial. *Curr Ther Res Clin Exp.* 2003;64(1):21-31.
11. Winther K, Apel K, Thamsborg G. A powder made from seeds and shells of a rose hip subspecies (*Rosa canina*) reduces symptoms of knee and hip osteoarthritis: a randomized, double blind, placebocontrolled trial. *Scand J Rheumatol.* 2005;34:302-308.
12. Von Krüedener S, Schneider W, Elstner EFA combination of *populus tremula*,*solidago virgaurea* and *fraxinusexcelsior* as an anti-inflammatory and antirheumatic drug. *Arzneimittelforschung.*1995;45(2):169-171.
13. Lucy Chen; Andreas Michalsen. Management of chronic pain using complementary and integrative medicine. Management of chronic pain using complementary and integrative medicine. *BMJ: British Medical Journal*, Vol. 357 (24 Apr 2017 - 30 Apr 2017).
14. Willich SN, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. *Phytomedicine* 2010;17:87-93. doi:10.1016/j.phymed.2009.09.003 pmid:19818588.
15. 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;26:1719-25. doi:10.1002/ptr.4639 pmid:22407780.
16. Lanhers MC, Fleurentin J, Mortier F, et al. *Planta Med.* 1992;58(2):117-123.
17. Eichler O, Koch C. *Arzneimittelforschung.* 1970;20:107-109.
18. Erdos A, Fontaine R, Friehe H, et al. *Planta Med.* 1978;34(1):97-108.
19. Uchida S, Hirai K, Hatanaka J, et al. *Biol Pharm Bull.* 2008;31(2):240-245.
20. Mahomed IM, Ojewole JA. *Phytother Res.* 2004;18(12):982-989.
21. Andersen ML, Santos EH, Seabra Mde L, et al. *J Ethnopharmacol.* 2004;91(2-3): 325-330.
22. Hansel R., Keller K., Rimpler H., Schneider G. (1992). *Hagens Handbuch der pharmazeutischen Praxis/ 5th Ed., Vol. 4, Drogen A-D.* Springer-Verlag, Berlin Heidelberg New York: 817-831 (a); 342-357 (b); 272-280 (c); 660-68 (d).
23. Blumental M., Hall T., Goldberg A. et al. (eds) .(2003). *The ABC Clinical Guide to Herbs.* Austin, TX: American Botanical Council.