

Pharmacist's Evaluation of Natural Ingredients in Topical Products for Rheumatoid Arthritis

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Abstract

Inflammatory diseases such as rheumatoid arthritis (RA) can lead to chronic pain and joint deformity. First line treatment includes disease-modifying antirheumatic drugs (DMARDs) to slow disease progression, but RA patients are often left with debilitating symptoms. This article explores alternative topical and naturally based options to treat RA symptoms, with supporting evidence for their use. Considered options include *Aloe vera*, Perillyl Alcohol (POH), *Aleurites moluccana*, *Calendula officinalis* extract (quercetin), *Achyranthes* species, Guizhi Shaoyao Zhimu, Curcumin (turmeric), Wutou, Radix paeoniae extract (Paeoniflorin), *Tripterygium wilfordii* Hook F (TWHF), Capsaicin, Cannabinoids (CBD), and Berberine. Many of these products show promising data for supplemental treatment of RA through various mechanisms, with CBD and TWHF having the most robust evidence supporting their use.

Keywords

Rheumatoid Arthritis, Natural Ingredient, Topical Treatment, Anti-Inflammatory, Alternative Treatment

1. Introduction

Rheumatoid arthritis (RA) is a complex autoimmune disorder in which a patient's immune system mistakenly attacks their healthy joints [1]. The etiology of RA is uncertain with theories claiming that both the environment and genetics play a role in its development. The pathophysiology of RA involves a disruption in the synovial cells that line a person's healthy joint [2].

In a healthy joint, fibroblast-like synoviocytes (FLS) are the predominant cells that interact to create an extracellular matrix [3]. These cells intrinsically develop a two-to-three-layer synovial lining that results in a healthy joint [3]. In RA,

macrophages invade the synovium and produce inflammatory biomarkers including growth factors, pro-inflammatory cytokines, and chemokines [3]. These markers activate the FLS cells resulting in further release of additional inflammatory markers such as IL-6 and prostanoids [3]. This potentiates inflammation of the synovium within the joint and leads to the destruction of the extracellular matrix [3].

A vicious cycle of inflammation ensues, resulting in destruction of the healthy joint and ultimately an activation of osteoclasts to destroy the bone [4]. The destruction of bone and joint majorly impacts a patient's day-to-day activities and can eventually become debilitating. The most commonly impacted joints include the hands, wrists, and knees, and a patient may experience morning stiffness, chronic pain, balance issues, and physical deformity of the joint impacted [1].

As inflammatory mediators invade and destroy the joint, this often leads to the production of autoantibodies. Specifically, rheumatoid factors and anti-citrullinated peptide antibodies are produced and are measured when diagnosing RA [4]. Other diagnostic criteria include the number of joints impacted by synovitis, symptom duration, C-reactive protein (CRP) values, and erythrocyte sedimentation rate (ESR) [5].

Following the diagnosis of RA comes management of the disease, for which earlier treatment leads to better outcomes [6]. The goal of treatment is to slow the disease progression and prevent deformity [7]. This is typically done using prescribed medications such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide [8]. These agents fall under the disease-modifying antirheumatic drug (DMARDs) category and are considered first-line treatment options in most patients [8]. In addition, various biologic response modifiers can be added on to DMARDs as part of second-line treatment [8]. These options include Remicade, Humira, Enbrel, Rituxan, Actemra, tofacitinib, and many more [8]. Outside of slowing down progression, reducing pain and disability is an important part of RA treatment. Strategies to reduce RA pain may include exercise, maintaining a healthy weight, over the counter pain relievers, acupuncture, hot and cold packs, and massage [1].

The purpose of this article is to explore alternative topical and naturally based options to treat RA. The following literature review is a comparison of the literature to support the use of 13 different natural products for the treatment of rheumatoid arthritis and its accompanying symptoms. Articles included in this review evaluated both oral and topical application of natural products in rheumatoid arthritis and were published in 1991-2022. Trials included in this review were *in-vitro*, *in-vivo*, randomized-controlled trials, animal models, clinical reviews, systematic reviews, meta-analyses and randomized clinical trials.

2. Comparison of Natural Topical Ingredients to Treat RA

2.1. *Aloe vera*

Aloe vera gel has been thought to potentially have a role as a topical agent in RA

due to its anti-inflammatory properties [9]. In a study performed by Subhashis *et al.* [10], heat-induced hemolysis of red blood cells (RBC) and hypotonicity-induced hemolysis of RBC were evaluated in rats receiving an *aloe vera* homogenate. These specific measures were chosen because lysis of lysosomal vesicles results in the release of enzymes that can induce an inflammatory response, which is the main driver of RA. Inhibiting lysis of the membrane has the potential to reduce the progression of inflammation. Concentrations of *aloe vera* homogenate used were 600, 800 and 1000 ug/mL of gel. Topical indomethacin served as a comparator within this trial. Results of the study [10] indicate that *Aloe vera* protects human RBCs from hypotonicity-induced hemolysis with the most protective effect at 1000 ug/mL. The percentage of inhibition was 74.89% at 1000 ug/mL, which was similar to that of indomethacin (80.52%). *Aloe vera* also proved efficacious in inhibiting heat-induced hemolysis in RBC, however was about half that of indomethacin (20.86% vs 43.98%). The results of this study [10] indicate a potential benefit of *Aloe vera* gel in reducing inflammation, and *Aloe vera* is a widely available product that can be bought in stores or grown at home.

2.2. Perillyl Alcohol (POH)

Perillyl Alcohol (POH) is a plant-based compound that has some data to support its use as a topical agent in rheumatoid arthritis. One *in-vitro/in-vivo* study [11] looked at the topical application of POH in arthritic rats. The *in-vitro* results indicated that POH suppressed reactive oxygen species and other signals that regulate stress and inflammation pathways. In addition, pro-inflammatory cytokine levels decreased after administration of POH ultimately resulting in a decrease in inflammation. Paw volumes, histological evaluation, and X-ray reports were utilized and aided in identification of a decrease in inflammation and bone erosion. While the results of this study [11] are promising, an increased number of trials are needed to recommend POH for the treatment of RA.

2.3. *Aleurites moluccana*

Aleurites moluccana leaves have been used for decades in the treatment of asthma, hepatitis, headache, and inflammatory processes [12]. The main anti-inflammatory mechanism of *A. moluccana* is thought to be a reduction in leukocyte migration, leading to decreasing numbers of cytokines and chemokines [13]. Mendes Hoepers *et al.* [13] sought to evaluate topical anti-inflammatory properties of *A. moluccana* in mice. Ear edema was induced utilizing croton oil to simulate inflammation. A semisolid dosage form of *A. moluccana* was instilled into the ear of the mouse and levels of tumor necrosis factor (TNF), interleukin-1b (IL-1b), and chemokine keratinocyte chemoattractant (CXCL1/KC) were measured. TNF, IL-1b, and CXCL1/KC are all indicators of pro-inflammatory processes. In evaluating CXCL1/KC, IL-1b, and TNF levels, significant reductions were observed at 62.29%, 38.36% and 53.75% respectively. Reduction in edema

was also observed and compared to a positive control of dexamethasone. It was found that *A. moluccana* reduced edema by 35.77% in comparison to 97.62% with dexamethasone. Ultimately this study [13] demonstrated the topical anti-inflammatory effects of *A. moluccana* through multiple mechanisms.

2.4. *Calendula officinalis* (Marigold) Extract: Quercetin

Calendula officinalis, commonly known as marigold, is a traditional medicine known for its potent anti-inflammatory activity when taken orally [14]. Little data delves into the topical anti-inflammatory properties of *Calendula officinalis*. A single study out of Romania [15] assessed the anti-inflammatory effect of a topical formulation containing diclofenac, methyl salicylate and lyophilized *Calendula officinalis* in rheumatoid arthritis. One-hundred and fifteen participants were included in this randomized, prospective study and were assigned to either active or placebo groups. The topical application was given twice a day for 14 days and Visual Analogue Scale (VAS) and ultrasound were utilized to measure outcomes such as pain throughout the 14 days of the trial. The baseline VAS score for both the active and placebo group was approximately 6 in patients with shoulder pain attributed to RA. By the 14th day, the experimental group had a VAS score of 2.36 vs placebo at 5.48 and was statistically significant. Ultrasound was used to assess differences in the thickness of the synovial membrane. At baseline, the synovial membrane thickness in the shoulder was about 3.3 mm in both active and placebo groups. At day 14, the active group had a synovial thickness of 1.32 vs 3.2 in the placebo group, which was statistically significant, and a 59% decrease in the thickness of the synovium. The results of this study¹⁵ are promising if there were to be an NSAID/methyl salicylate/*Calendula officinalis* topical formulation, however, there is no direct evidence that topical *Calendula officinalis* can be utilized as monotherapy as an option for RA.

2.5. *Achyranthes* Species

Achyranthes is a flowering plant used in Chinese medicine as an antiviral, anti-inflammatory, and analgesic agent [16]. Immunohistochemistry in arthritis models have shown that *Achyranthes* inhibits the effects of IL-6-mediated matrix metalloproteinases [17]. *In-vivo* models have showcased a decrease in cartilage erosion, subchondral plate thickness, cartilage degeneration, and synovium inflammation [17]. In an animal model, *Achyranthes* proved to decrease paw swelling, bone degradation, as well as the proliferation of inflammatory cells [18]. No topical studies have been performed using *Achyranthes*, so the effects of using *Achyranthes* species for the topical treatment of RA remain unknown.

2.6. Guizhi Shaoyao Zhimu

In Chinese medicine, Guizhi Shaoyao Zhimu decoction is considered a first line therapy in the treatment of RA [19]. An *in-vivo* model evaluated toe swelling, arthritis score, and inflammatory cytokine levels in collagen-induced arthritis

(CIA) rats [20]. The results of the study demonstrated a reduction in both toe swelling and arthritis score. Serum levels of various inflammatory cytokines, including TNF-alpha, IL-1B, IL-6 and IL-17a, all decreased with Guizhi Shaoyao Zhimu *in-vivo* administration. There is no data to support the use of Guizhi Shaoyao Zhimu topically; however it is still widely used outside of Western medicine.

2.7. Curcumin (Turmeric)

Curcumin is an active compound found in turmeric, which is a common spice that has been used for centuries in cooking and traditional Chinese medicine [21]. Turmeric has an abundance of oral data showcasing an anti-inflammatory effect which has sparked interest in its research [21]. Little data evaluating topical turmeric as an anti-inflammatory exists. Future research should address the topical role of turmeric in inflammatory conditions, as currently there is no evidence to suggest its effectiveness when used topically.

2.8. Wutou

Wutou decoction is a common preparation used in Chinese medicine for the treatment of RA. When given orally via decoction, Wutou has showcased an inhibition of NF-kB mediated inflammatory response in a CIA rat model [22]. When administered intragastrically, wutou lowered swelling in the hind paws of rats with RA, in addition to ROS suppression [23]. These studies demonstrate the effectiveness of wutou for reducing inflammation when used orally, but more studies are necessary to see these effects for topical use.

2.9. Radix Paeoniae: Paeoniflorin

Paeoniflorin is the major active compound of total glycoside of paeony which is traditionally extracted from the Chinese Peony flower in traditional Chinese medicine [24]. It has been used to treat pain and inflammation over thousands of years. When injected into animal models with collagen induced arthritis, joint destruction was suppressed [25]. In addition, a decreased arthritis score, ankle/paw swelling, and suppression of the proliferation of FLS, T, and B lymphocytes was observed [25]. Decreases in reactive oxygen species and proinflammatory cytokines and chemokines were also observed [25]. While this ancient flower has been used over the years, there is no data to support its use as a topical agent in RA.

2.10. *Tripterygium wilfordii* Hook F

Tripterygium wilfordii Hook F (TWHF) is a traditional Chinese herb that has been used for thousands of years in the treatment of joint pain [26]. Its mechanism of action is thought to work through an inhibition of adhesion molecules, matrix metalloproteinases, and pro-inflammatory cytokines and mediators, in addition to inducing apoptosis of lymphocytes and synoviocytes ulti-

mately inhibiting their proliferation [26]. Recently, TWHF has been studied as a topical agent in RA due to reproductive side effects associated with its oral use [26]. Cibere *et al.* [27] conducted a 6-week, randomized, double blind placebo controlled trial with 61 RA patients that used intention-to-treat analysis. The primary outcome was a modified American College of Rheumatology-20 (ACR-20) criteria response rate. Secondary outcomes focused on tenderness, swollen joint count, and morning stiffness. The odds of achieving a modified ACR response was 8.1 in the TWHF group when compared to placebo. TWHF was successful in reducing tender and swollen joint count and morning stiffness. Two other studies that included nearly 250 patients found similar results to that of Cibere *et al.* [28] [29]. Improvement in tender joint and swollen joint count was observed in addition to a higher ACR50 response among patients using TWHF. Self-reported joint pain relief in a study conducted by Jiao *et al.* [29] was 90.8% in the TWHF group in comparison to 69% in the placebo group. Minimal adverse events were noted with the topical application of TWFH with the most common of skin allergy, which was not significantly different from what was observed in the placebo group [28] [29]. These randomized, double blind, placebo-controlled trials showcase promising data for the topical use of TWHF in RA patients.

2.11. Capsaicin

Capsaicin is a common over-the-counter cream that is recommended for various types of pain, mainly neuropathic [30]. Capsaicin has an anti-inflammatory mechanism of action that works by depleting substance P [31]. By activating the TRPV1 receptor every day with the application of capsaicin, substance P becomes depleted and the nociceptors no longer respond to stimuli [32]. Substance P is commonly implicated in the pathogenesis of inflammation and pain making this a strong target for RA pain [31]. Data for capsaicin specifically in RA patients is not robust and showcases minimal benefit. One review included various studies that favored capsaicin over placebo in the treatment of RA pain [33]. However the review concluded that while this data may favor capsaicin, the evidence is weak to support its ability to treat RA pain. Ultimately, capsaicin's minimal side effect profile makes it an option for add-on therapy in patients with persistent pain and an inadequate response to other topical agents. The main side effect associated with capsaicin is its local burning sensation upon its application due to it being derived from chili peppers. Overall, capsaicin may be a good option for patients who have not experienced relief from other topical agents and who are capable of handling the side effects associated with application.

2.12. Cannabidiol

Cannabidiol (CBD) is a natural ingredient of interest for treating a large number of conditions due to its anti-inflammatory action [34]. CBDs' anti-inflammatory

action is complex and works through activation of the endocannabinoid system, specifically the cannabinoid type 1 and 2 receptors [34]. Activation of these receptors decreases cytokine production and immune cell mobilization [34]. While data is more robust for the oral use of CBD in inflammatory conditions, new research has begun exploring the role of CBD as a topical agent. Topical administration of CBD bypasses its poor oral bioavailability, gastrointestinal side effects, and any concerns that CBD may impact higher brain function [35]. A study performed by Hammell *et al.* [35] utilized a mouse model to evaluate the role of transdermal CBD in reducing inflammation and pain in arthritis. Results showcased a significant reduction in joint swelling at day 4 in addition to improvements in limb posture scores which included spontaneous pain, immune cell infiltration, and thickening of the synovial membrane. A dose-dependent reduction in pro-inflammatory biomarkers was also seen in this study. Major side effects have not been reported with the topical use of CBD. As such, CBD is a promising option for patients to reduce RA pain, and is often recommended as a natural option for symptom relief.

2.13. Berberine

Berberine is an alkaloid isolate that can be extracted from a variety of plants such as *Berberis vulgaris*, *Mahonia aquifolium*, and *Coptidis Rhizoma*. Berberine has been used for centuries in Chinese medicine and is thought to have antibiotic, antitumor, antiplatelet, and anti-inflammatory properties [36]. Various *in vitro* and *in vivo* studies have showcased berberine's potential benefit in treating symptoms associated with RA. One study found that berberine can suppress synovial joint inflammation via inhibition of FLS, one of the major contributors to the worsening of RA [38]. Another cell culture study identified that IL-21 could induce autophagy which would ultimately promote proliferation of the FLS cells [37]. Berberine was able to block the induction of autophagy therefore blocking the proliferation of FLS. Berberine's role in targeting FLS, a major component of RA pathogenesis, has been elucidated in culture data and showcases its potential therapeutic effect. Culture data is difficult to use in support of berberine as the topical use of berberine would face the major issue of absorption through the skin. A study conducted by Elkomy *et al.* [39] evaluated the topical use of berberine. Specifically, this study looked at boosting the transdermal system of berberine by encapsulating it in chitosan, a surface-modified bilosome nanogel. A rat model was used and both *ex-vivo* and *in-vivo* models were utilized. The *ex-vivo* model looked at the permeation of the compound with the enhanced liposome and found that this modality enhanced permeability and extended the release time of berberine. This could be potentially useful when formulating topical berberine for over-the-counter use in order to ensure its adequate absorption through the skin. The *in vivo* portion of this study assessed paw edema, to which a 24.4% reduction was seen at the 12-hour time point. While the data for topical berberine is limited and there have not been any studies conducted on humans, the

relatively benign safety profile of berberine makes it a potential adjuvant product for RA.

3. Discussion

Alongside typical medications used to slow the progression of RA such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, there are a range of natural products that are used to aid in relieving symptoms such as inflammation and pain. Many of the natural ingredients listed above work to produce anti-inflammatory effects through different mechanisms that can alleviate symptoms of RA. Although there are several studies that have been done in these natural products, there are some notable limitations to these studies.

One major limitation is that many of the studies were conducted in animals and lack human trials, which makes it difficult to infer that these topical formulations will be efficacious in humans. However, some of these natural ingredients have been used for years in countries outside of Western medicine. Although often the mechanism of action remains unknown, historic use of products such as Wutou, Guizhi Shaoyao Zhimu, curcumin, and TWHF supports their healing benefit.

Calendula officinalis demonstrated significant anti-inflammatory properties in its trials, which showed that this natural product may have promising effects in the relief of RA symptoms. However, it was not used as a singular ingredient in its studies. *Calendula officinalis* was used with diclofenac and methyl salicylate as a topical application, and the trial results exemplified reduced synovial membrane thickness. *Calendula officinalis* used as a single product alone has not been proven to help with RA symptoms or disease modification. In order to decipher whether *Calendula officinalis* has significant anti-inflammatory effects, there must be more studies done with this herbal remedy independently.

Another natural product that has the potential to help with RA symptoms is *Achyranthes*, as trials demonstrate that it can decrease cartilage erosion, subchondral plate thickness, cartilage degeneration, and synovial inflammation in animals. Wutou decoction, which is a topical preparation used in Chinese medicine, is also promising as it can decrease inflammatory response. Radix paeoniae, which comes from the white peony, works to decrease inflammation when administered orally, but there is no evidence that the topical formulation would be sufficient for RA symptom relief. Other topical herbal ingredients that may have data for use in rheumatoid arthritis include perillyl alcohol, *aleurites moluccana*, curcumin, Guizhi Shaoyao Zhimu, and berberine.

CBD has also had many studies in humans for different conditions and shows promising reduction in inflammation, however, more studies should be conducted to determine the full benefit of CBD in the use in RA specifically. This is also the case for the common over-the-counter topical product capsaicin, which is typically used to treat pain. Capsaicin could be an efficacious product for use as an add-on to traditional therapy, but may not provide sufficient pain relief for

RA on its own.

TWHF trials on human models have been conducted and could be promising for the treatment of symptoms associated with rheumatoid arthritis. This herbal remedy significantly reduced tender and swollen joints as well as morning stiffness. Since this product has had human trials and shows promising data, TWHF could be a reasonable natural topical product to use in RA.

4. Conclusion

Rheumatoid arthritis can become a debilitating disease as a patient's immune system mistakenly attacks healthy joints and causes destruction. There are several manufactured medications that help modify RA disease such as methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide, but many patients are left with symptoms such as physical deformity, chronic pain, and morning stiffness. These symptoms can often become debilitating and significantly impact someone's quality of daily life. In many non-Western medicine cultures, people use natural ingredients to alleviate these symptoms caused by rheumatoid arthritis. Natural ingredients have a supplemental role in RA as many of them work to decrease the inflammatory response caused by the disease. Even though many of these topical ingredients show promising data for anti-inflammatory effects and symptom relief, trials in human models are severely lacking. Overall, natural ingredients show a promising future for the alleviation of symptoms associated with rheumatoid arthritis, and there are several products featuring these ingredients that may be recommended.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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