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A REVIEW ON HERBAL OINTMENT AS A POTENTIAL ALTERNATIVE TO METHOTREXATE FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

And therapeutic potential of herbal formulations in the treatment of rheumatoid arthritis. **Rheumatoid Arthritis (RA)** is a chronic autoimmune and inflammatory disorder characterized by persistent joint inflammation, pain, swelling, and progressive destruction of cartilage and bone. If left untreated, RA can lead to severe joint deformity, reduced mobility, and involvement of other organs. The prevalence of RA continues to increase globally, including in India, where millions of individuals are affected. Early diagnosis and effective management are therefore essential to prevent disease progression and improve the quality of life of patients. Conventional treatment strategies primarily include **disease-modifying anti-rheumatic drugs** (DMARDs) such as **Methotrexate**, which is considered the anchor drug in RA therapy. Methotrexate acts by inhibiting folate metabolism and modulating inflammatory pathways, thereby reducing immune-mediated joint damage. However, long-term use of methotrexate may lead to several adverse effects including hepatotoxicity, gastrointestinal disturbances, and bone marrow suppression. These limitations have encouraged researchers to explore safer and more effective alternative therapies. Herbal medicines have gained considerable attention due to their natural origin, lower toxicity, and multiple therapeutic actions such as anti-inflammatory, antioxidant, and immunomodulatory effects. Several medicinal plants including ***Azadirachta indica***, **Allium sativum**, **Aloe vera**, **Vitex negundo**, and ***Boerhavia diffusa*** contain bioactive phytochemicals that help reduce inflammation and alleviate joint pain associated with RA. Herbal formulations, particularly topical ointments, may provide localized therapeutic effects with fewer systemic side effects compared to synthetic drugs. This review paper discusses the pathophysiology, prevalence, and current treatment strategies for **Rheumatoid Arthritis**, along with the mechanism and limitations of **Methotrexate** therapy. Furthermore, it highlights the potential role of selected medicinal plants and herbal ointment formulations as alternative or complementary approaches for the management of RA. The review emphasizes the need for further scientific studies to validate the safety, efficacy.

KEYWORDS: Anti-inflammatory, Rheumatoid Arthritis, Herbal Ointment, Methotrexate.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which the body's immune system mistakenly attacks its own joints, causing inflammation. It mainly affects the lining of joints (synovium), leading to pain, swelling, stiffness, and sometimes joint deformity over time.

Key Points

- Type of disease: Autoimmune and inflammatory disorder
- Mainly affects: Joints such as the hands, wrists, knees, and feet
- Nature: Chronic (long-lasting) and progressive if untreated
- Common symptom: Morning stiffness lasting more than 30–60 minutes

What Happens in the Body

In RA, the immune system attacks the synovial membrane (joint lining). This causes:

- Persistent inflammation
- Thickening of the synovium
- Damage to cartilage and bone
- Gradual loss of joint function

Common Symptoms

- Joint pain and swelling
- Stiffness, especially in the morning
- Warmth and redness around joints
- Fatigue and weakness
- Sometimes fever or weight loss

What is More Affected?

- Most common between 30–60 years of age
- Women are affected more than men
- Risk increases with family history, smoking, and certain infections

If RA is not treated early, it can cause:

- Permanent joint damage
- Reduced mobility
- Involvement of other organs such as lungs, heart, and eyes

Management Overview

RA can be well controlled with:

- Medications
- Physiotherapy
- Early diagnosis and treatment

Current medical strategy

National Prevalence & Forecasts (2025–2026)

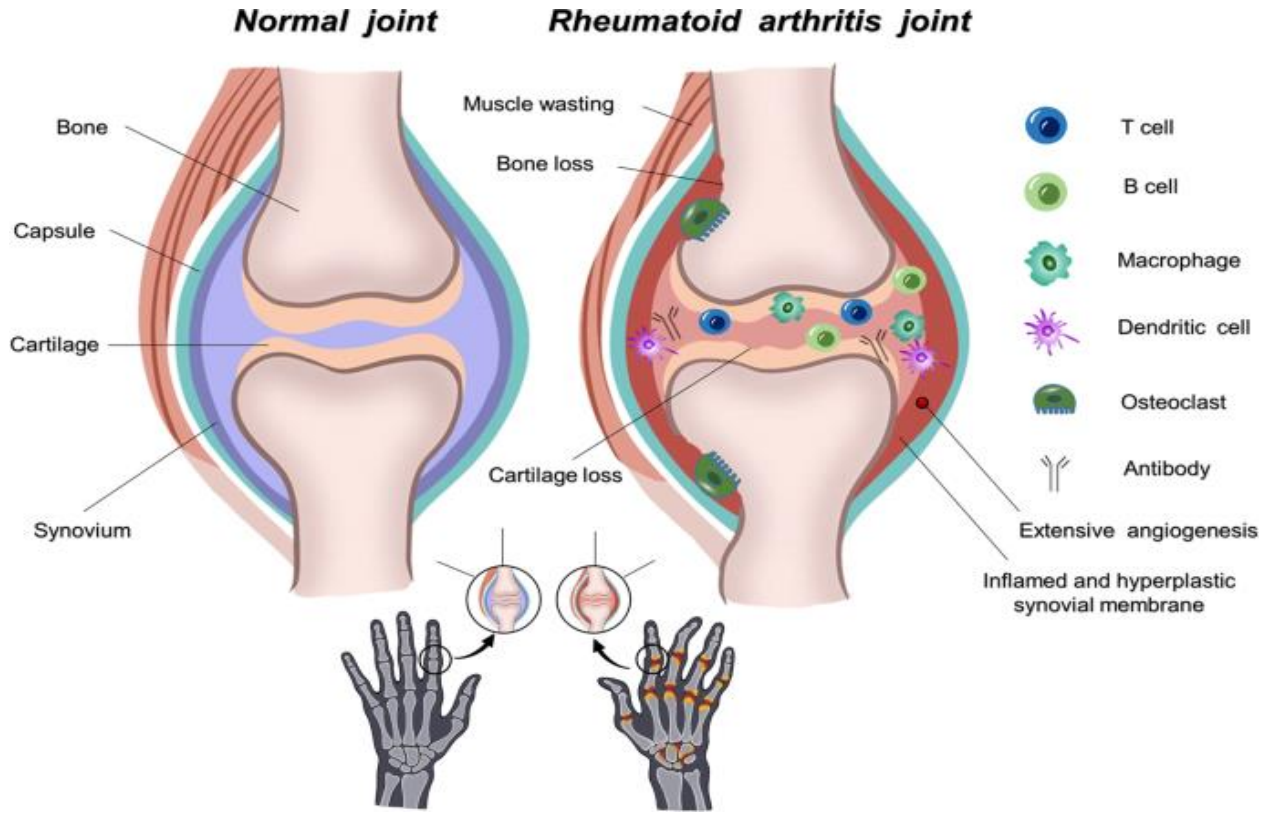
Recent studies and forecasts based on the Global Burden of Disease (GBD) data provide a clear picture of the RA landscape in India.

Total Affected Population: As of 2025, it is estimated that 4.22 million to 7 million individuals in India live with RA.

Adult Prevalence Rate: Approximately 0.92% of Indian adults are affected by RA.

Trend Forecast (2022–2036): Predictive modeling (ARIMA) suggests a steady upward trend in both incidence and Disability-Adjusted Life Years (DALY) through 2026, with cases growing at an annual rate of approximately 1.36%.

The best rheumatoid arthritis treatment options in 2026 go far beyond symptom control. With advancements in DMARDs, biologics, targeted therapies, and regenerative medicine, patients now have access to comprehensive, personalized care that slows disease progression and preserves joint function.



Methotrexate in treatment of rheumatoid arthritis

Mechanism

Although there has been development of numerous new targeted therapies for rheumatoid arthritis (RA) in recent years, methotrexate has remained the "anchor drug" for most patients since the late 1980s. However, despite its long-term and widespread use for RA, the precise mechanism of this drug remains elusive.

Methotrexate was originally designed as a folate pathway antagonist by inhibiting dihydrofolate reductase (DHFR) when given at very high doses for leukaemia (as high as 1 gram in a single dose), but it was found that at much lower doses (15–25 mg weekly) the drug was effective in RA patients.

The oncologic mechanism of action involves inhibition of purine synthesis and thus arrest in the S phase of the cell cycle eventually leading to apoptosis of cells. The clinical effects of high dose methotrexate used in cancer including the adverse effects can be reversed with high doses of calcium or folinic acid. On the other hand, the efficacy of low-doses of methotrexate used in RA patients is unaffected by the administration of folic acid and it is in fact almost invariably part of the RA medication regimen to minimize the unwanted methotrexate side effects. This indicates that inhibition of purine metabolism is unlikely to be the major mechanism of methotrexate in RA and that another element must be accounting for efficacy of methotrexate in RA patients.

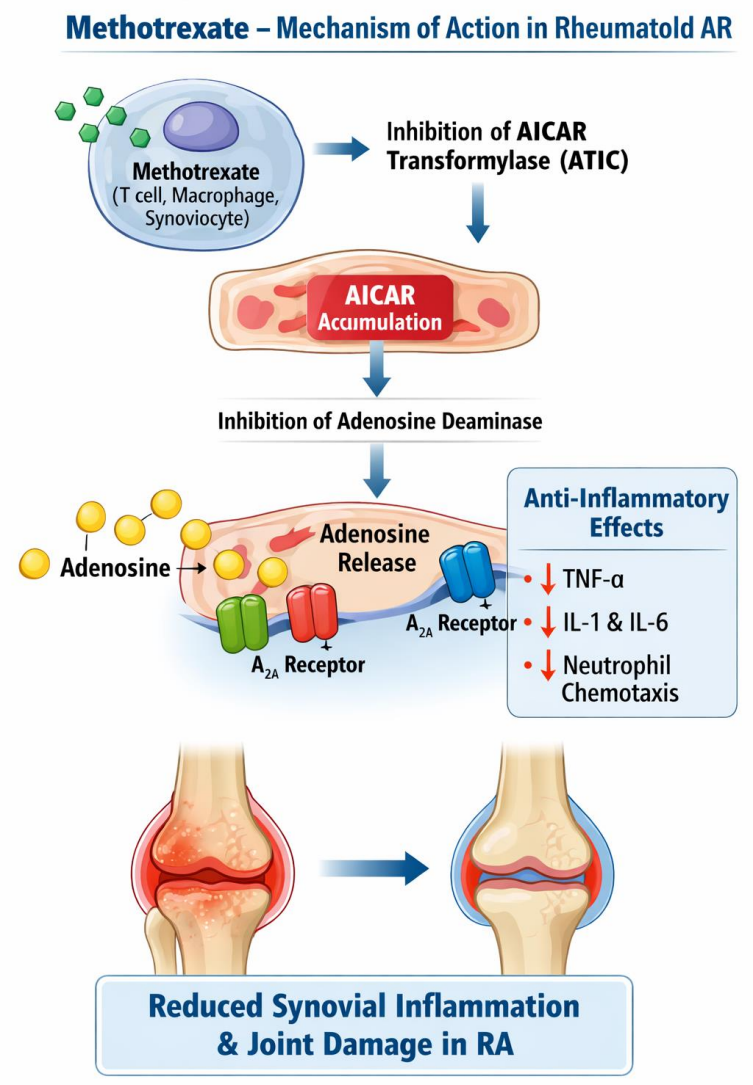
Mechanism of methotrexate toxicity

While methotrexate remains first line treatment and is effective in mainly RA patient it has certain side effects that can be helpful to further explain its mechanistic effects. Methotrexate can lead to hepatic fibrosis in some cases, and this may be secondary to reduction in hepatic folate st**ores and accumulation of polyglutamated methotrexate.**

Additionally, ethanol ingestion (known as a common cause of cirrhosis) has been shown to induce release of plasma levels of adenosine. In ex vivo hepatic slices, methotrexate led to increased adenosine levels; adenosine can stimulate matrix protein production by stellate cells and notably mice deficient for the A2A receptor but not wildtype or A3 knockouts are more resistant to developing fibrosis in a carbon tetrachloride challenge. One positive side effect of increased matrix protein formation is that adenosine can promote excisional wound healing by increasing interstitial matrix. Methotrexate induced nodules in RA patients are formed from monocyte differentiation into multinucleated giant cells. In vitro monocytes can be induced to form giant cells by phorbol myristate acetate stimulating both differentiation and fusion of the giant cells. It was shown that adenosine acting via the A1 receptor does lead to formation of multinucleated giant cells.

There have been numerous studies over the years regarding the use of folic acid or folinic acid supplementation to reduce methotrexate toxicity and its effect on methotrexate efficacy in RA. A meta-analysis in 2013 demonstrated that supplementation with either daily folic acid or weekly folinic acid significantly reduced the incidence of gastrointestinal side effects, elevation in serum transaminase levels, and reduction in discontinuation of methotrexate for any reason. Many physicians who use methotrexate as a treatment will begin with folic acid and potentially attempt to switch to folinic acid to reduce adverse effects, however there is no clear evidence indicating that folinic acid is superior to folic acid in this regard. Folic acid, unlike weekly folinic acid, is given daily and does not compete with methotrexate cellular uptake via the reduced folate carrier. Folinic acid is generally dosed weekly on the same day as weekly methotrexate and is given approximately 10–12 hours after methotrexate to allow for unopposed uptake of methotrexate.

A number of studies have shown that supplementation with folic acid decreases toxicity yet does not alter the efficacy of methotrexate based on RA disease activity parameters including tender or swollen joint count or physician's global assessment score. This continued efficacy of methotrexate for RA in the presence of folic or folinic acid is one reason that alternate mechanisms for RA efficacy such as increased adenosine signaling are favored by many over the inhibition of folate metabolism.



Comparison table between Herbal Ointment and Methotrexate Ointment

Parameter	Herbal Ointment	Synthetic Methotrexate Ointment
Source	Prepared from medicinal plants such as Tinospora cordifolia, Curcuma longa, and Asparagus racemosus	Prepared from synthetic drug Methotrexate
Nature	Natural formulation containing phytochemicals	Synthetic chemical formulation
Side Effects	Usually, fewer side effects and less skin irritation	May cause redness, irritation, dryness, or systemic toxicity
Therapeutic Action	Shows multiple actions like anti-inflammatory, antimicrobial, antioxidant, and wound healing	Mainly acts as immunosuppressant and anti-inflammatory
Toxicity	Generally low toxicity when used properly	Long-term use may cause toxicity
Cost	Economical due to plant-based raw materials	Relatively expensive
Patient Acceptance	Higher acceptance due to natural origin	Some patients avoid due to potential adverse effects
Safety for Long Use	Usually safer for long-term topical use	Long-term use requires medical supervision

MATERIALS AND METHOD

Sr. No.	Materials	Role
1	*Azadirachta indica* (Neem)	Reduces joint inflammation and swelling due to its strong anti-inflammatory and immunomodulatory properties.
2	*Allium sativum* (Garlic)	Helps decrease inflammatory cytokines and oxidative stress, thereby reducing joint pain and stiffness.
3	*Aloe vera*	Provides anti-inflammatory and soothing effects that help relieve joint pain and irritation.
4	*Vitex negundo* (Nirgundi)	Exhibits analgesic and anti-arthritic activity, helping to reduce pain, swelling, and joint stiffness.
5	*Boerhavia diffusa* (Punarnava)	Reduces joint swelling and inflammation due to its anti-inflammatory and immunomodulatory properties.
6	White soft paraffin	Ointment base
7	Hard paraffin	Stiffening agent
8	Cetostearyl alcohol	Emulsifying agent and Stabilizing agent
9	Methyl Paraben	Preservative
10	Distilled Water	Vehicle/Solvent

Method of Preparation

Step 1: Preparation of Herbal Extract

1. The plant materials (Neem leaves, Garlic bulb(cloves), Aloe vera gel,Nirgudi root, Punarnava whole plant) were cleaned, shade-dried, and coarsely powdered.
2. Equal quantities of the powdered drugs were mixed thoroughly.
3. The mixed powder was boiled with distilled water on a water bath for 30–45 minutes to prepare an aqueous extract.
4. The extract was filtered using muslin cloth and concentrated to obtain a thick extract.

Step 2: Preparation of Ointment Base (Fusion Method)

1. White soft paraffin, hard paraffin, cetostearyl alcohol, and lanolin were accurately weighed.
2. The ingredients were melted in descending order of their melting points using a water bath.
3. The molten base was stirred continuously to ensure uniform mixing.

Step 3: Incorporation of Herbal Extract

1. The concentrated herbal extract was slowly added to the molten ointment base with continuous stirring.
2. Stirring was continued until a uniform and homogeneous ointment was obtained.
3. The ointment was allowed to cool while stirring gently.

Step 4: Packing

The prepared herbal ointment was transferred into clean, dry, and labelled ointment containers.[15]

Evaluations

Sr. No.	Evaluations	Procedures
1	Physical Evaluation Colour Odour Consistency Homogeneity	Observed visually Characteristic Smooth and uniform Checked by visual inspection for lumps or grittiness
2	pH Determination	1 g of ointment was dispersed in 100 ml of distilled water. The pH was measured using a digital pH mater.

		Ph was measured using a digital pH meter. Ph suitable for skin application indicates safety topical use.
3	Spreadability Test	A measured quantity of ointment was placed between two glass slides. A known weight was applied on the upper slide.
4.	Skin irritation Test	The ointment was applied on a small area of skin. The site was observed for 24 hours for redness, itching, inflammation. Absence of irriation indicates suitability for topical use.
5	Anti-Inflammatory Activity (In-vivo/Laboratory Model)	Anti-arthritic activity was evaluated using paw edema method or arthritis-induced animal model. The ointment was applied topically on inflamed joints. Reduction in swelling, redness, and joint stiffness was observed and compared with control
6	Pain Reduction and Joint Mobility	Improvement in joint movement and reduction in pain were observed after regular application. Decrease in joint stiffness indicates effectiveness against rheumatoid arthritis
7	Stability studies	The ointment was stored at different temperatures (room temperature and accelerated conditions).

CONCLUSION

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disorder that leads to progressive joint damage, pain, stiffness, and reduced mobility. Although conventional treatments such as Methotrexate remain the cornerstone of RA management, their long-term use is often associated with adverse effects including hepatotoxicity, gastrointestinal disturbances, and bone marrow suppression. These limitations highlight the need to explore safer and more effective therapeutic alternatives.

Medicinal plants have attracted significant attention due to their natural origin, availability, and multiple pharmacological activities such as anti-inflammatory, antioxidant, and immunomodulatory effects. Plants such as Azadirachta indica, Allium sativum, Aloe vera, Vitex negundo, and Boerhavia diffusa contain bioactive phytoconstituents that may help reduce inflammation, relieve joint pain, and improve joint function in patients with RA.

This highlights the potential of herbal ointment formulations as a topical therapeutic approach for the management of RA. Herbal ointments may provide localized treatment with reduced systemic side effects compared with conventional synthetic drugs. However, further experimental studies, clinical trials, and standardization of herbal formulations are necessary to establish their safety, efficacy, and therapeutic potential in the management of rheumatoid arthritis.

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