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Polyherbal Formulations for Rheumatoid Arthritis: An Ethnomedicinal and Pharmacological Review

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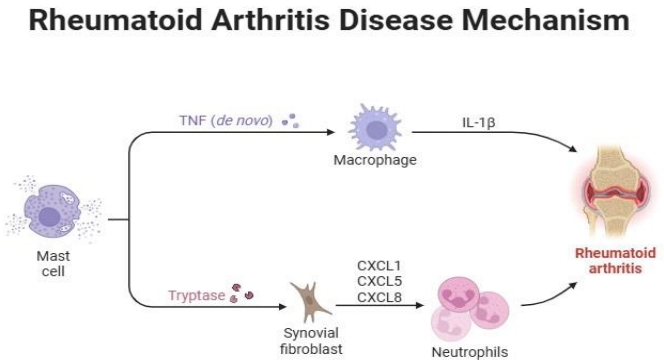
ABSTRACT

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disorder that affects millions worldwide, causing persistent joint pain, swelling, and reduced mobility. While conventional treatments like NSAIDs, corticosteroids, and biologics offer symptomatic relief, they often come with serious side effects and high costs, limiting long-term use. In recent years, there has been a renewed interest in polyherbal formulation combinations of multiple medicinal plants traditionally used in ethnomedicine as safer and potentially more effective alternatives for managing R A. This review explores the ethnomedicinal background and pharmacological relevance of various herbs commonly used in polyherbal formulations for RA. Plants such as Zingiber officinale (ginger), Curcuma longa (turmeric), Boswellia serrata (Indian frankincense), Withania somnifera (ashwagandha), and Tinospora cordifolia (giloy) have shown promising anti-inflammatory, antioxidant, and immunomodulatory effects. When combined, these botanicals may work synergistically to alleviate joint inflammation, reduce oxidative stress, and regulate immune responses, addressing the disease on multiple fronts. The review also highlights recent preclinical and clinical studies that validate the efficacy and safety of these formulations, along with the emerging role of novel drug delivery systems such as nano-carriers to enhance their bioavailability. Despite encouraging outcomes, challenges such as a lack of standardization, dosage precision, and mechanistic clarity remain. Overall, polyherbal formulations represent a promising, culturally rooted, and scientifically evolving approach to RA management. Further research focusing on quality control, pharmacokinetics, and long-term clinical efficacy could pave the way for integrating these therapies into mainstream healthcare.

Keywords: *Polyherbal formulations, Rheumatoid arthritis, Ethnomedicinal plants, Anti-inflammatory, Immunomodulatory, Herbal therapeutics.*



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1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that affects millions worldwide, significantly diminishing quality of life. Unlike osteoarthritis, which arises due to mechanical wear and tear, RA is rooted in immune system dysfunction [1]. In this condition, the body's defense mechanisms mistakenly target its own tissues, particularly the synovial membrane lining the joints. This leads to persistent inflammation, pain, swelling, stiffness, and, over time, joint deformity and reduced mobility. Left unmanaged, RA can cause severe functional impairment and disability [2].

RA primarily affects the small joints of the hands, wrists, and feet and is notably symmetrical, meaning it tends to impact both sides of the body equally [Figure 1]. Among its early and most distressing symptoms is morning stiffness. Patients often wake to find their fingers and joints swollen, numb, and stiff, making simple tasks like brushing teeth or holding a cup extraordinarily difficult. Although this stiffness may ease with movement, it reflects a deep-seated inflammatory process that continues to smolder even during rest [3].

However, RA is not limited to the joints alone. Its systemic nature allows the chronic inflammation to extend beyond the musculoskeletal system, potentially affecting the heart, lungs, eyes, skin, and even blood vessels [4]. As a result, many patients also experience general symptoms such as persistent fatigue, low-grade fever, and a constant feeling of malaise. These features underscore that RA is a multi-dimensional illness that requires a comprehensive, holistic treatment approach addressing both its localized and systemic manifestations [5].

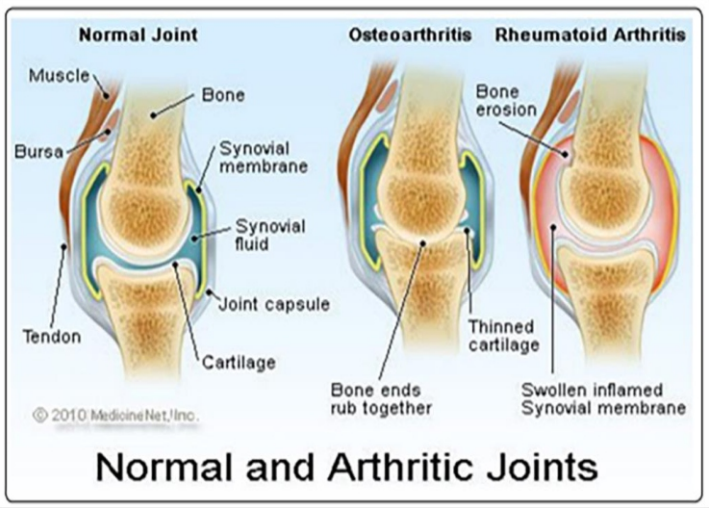

Figure 1. Normal and arthritic joints

1.1 The Need for Alternative Approaches in RA Management

Despite advances in pharmacotherapy, the long-term management of RA remains challenging. Conventional drugs such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) are effective in reducing inflammation and slowing disease progression. However, these medications are often associated with significant side effects ranging from gastrointestinal discomfort and liver toxicity to increased susceptibility to infections and cardiovascular risks, particularly when used over extended periods.

Given these limitations, there is increasing interest in complementary and alternative therapies, especially those that align with traditional healing practices and are perceived as safer for long-term use. Among these, polyherbal formulations have emerged as a promising therapeutic approach in RA management. These formulations are based on the synergistic use of multiple medicinal plants, each selected for its unique pharmacological properties that collectively aim to target various aspects of RA pathology.

1.2 Rationale for Polyherbal Formulations

RA is a multifactorial disease involving chronic inflammation, immune dysregulation, oxidative stress, and tissue destruction. This complexity implies that a single-drug or single-herb treatment might not sufficiently address the diverse mechanisms underlying the disease. Polyherbal formulations aim to overcome this challenge by combining different herbs that work through complementary pathways to achieve a broader therapeutic impact.

Each herb in a polyherbal formulation contributes distinct activities such as anti-inflammatory, antioxidant, immunomodulatory, or analgesic effects. Together, these actions may improve symptoms more effectively than isolated compounds. Moreover, the synergistic effect of such formulations allows for lower doses of each individual herb, potentially minimizing toxicity and side effects while enhancing efficacy.

Importantly, polyherbal strategies are rooted in traditional medical systems like Ayurveda, which have historically used herbal combinations to restore balance and health in chronic illnesses like arthritis. The modern revival and scientific evaluation of these approaches offer a way to integrate time-tested remedies with contemporary evidence-based medicine.

1.3 Emerging Scientific Evidence

Recent preclinical studies have provided encouraging data on the efficacy of polyherbal formulations in the treatment of RA. Animal models of arthritis have shown that certain polyherbal combinations can significantly reduce joint inflammation, improve inflammatory biomarkers, and prevent weight loss associated with chronic disease. For example, formulations containing *Glycosmis pentaphylla*, *Tridax procumbens*, and *Mangifera indica* have demonstrated notable reductions in joint swelling and systemic inflammation, sometimes showing effects comparable to standard drugs like indomethacin [6].

Topical polyherbal preparations such as gels and emulgels also show great potential. These formulations are particularly beneficial for patients who experience gastrointestinal sensitivity or cannot tolerate oral medications. Applied directly to the affected joints, they can provide localized relief from pain and inflammation with minimal systemic side effects.

One of the key advantages of polyherbal therapy is the synergistic action of its constituents. When herbs are used in combination, they often exhibit enhanced therapeutic activity compared to their individual components. This not only boosts effectiveness but also reduces the required dose of each herb, which can decrease the likelihood of adverse effects.

Furthermore, many polyherbal formulations have shown excellent safety profiles in preclinical toxicity studies, making them suitable for long-term use, a crucial consideration for managing chronic illnesses like RA. With minimal reported toxicity even at higher doses, these formulations offer a patient-friendly and sustainable option for ongoing symptom control [7].

In light of the complex pathology of rheumatoid arthritis and the limitations of existing pharmaceutical treatments, polyherbal formulations present a compelling, multi-targeted therapeutic approach. They offer a bridge between traditional medicinal wisdom and modern scientific validation, combining safety, efficacy, and patient acceptability. As scientific interest in natural products continues to grow, polyherbal strategies could play a transformative role in the integrative management of RA, offering hope to those seeking safer and more holistic relief from this debilitating disease [8].

This review looks at the rising interest in polyherbal mixtures as a possible way to manage rheumatoid arthritis (RA), an ongoing autoimmune disorder that makes joints swell and affects everyday living. Although mainstream medicines can help, they often bring side effects, spotty results, or hefty bills. For these reasons, many people, and some modern doctors, are once again turning toward safer, whole-body options rooted in traditional healing.

The review sets out to show how blending plants long used side by side in different cultures may offer a gentler, more cooperative strategy for easing RA symptoms. Northeastern India is highlighted, since that region's forested villages still rely heavily on herbal remedies, making its ethnomedicine a useful lens for the study.

Beyond customary wisdom, the article looks closely at each herb's chemistry, noting active compounds that calm inflammation, steady the immune system, and mop up damaging free radicals. It covers many product forms-often sips of brewed extract or soothing topical gels-explaining how they are put together, whether they work, and what safety tests say.

Finally, the review surveys lab trials and small human studies showing that these polyherbal mixes can ease pain and stiffness, with some data even putting their effects on par with leading anti-inflammatory drugs.

Throughout the paper, the authors keep circling back to herbal synergy, the idea that mixing certain plants can boost benefits and tone down unwanted reactions. Finally, they sketch out future research paths and stress the pressing need for solid clinical trials. Overall, they call for an integrated approach to rheumatoid arthritis treatment-one that honours age-old herbal traditions yet stands on firm modern science.

1.4 Limitations of Conventional RA Therapies

1. Burden of Side Effects in Conventional RA Management

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to relieve pain and inflammation in RA, but their prolonged use can irritate the gastrointestinal tract and increase the risk of ulcers, kidney dysfunction, and elevated blood pressure, especially in individuals with pre-existing health conditions. Corticosteroids offer rapid symptom relief, yet long-term use is associated with serious adverse effects such as osteoporosis, weight gain, mood swings, elevated blood glucose levels, and heightened susceptibility to infections. Disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, are effective in slowing disease progression. However, they can also suppress the immune system, making patients more vulnerable to infections, and may cause side effects including liver toxicity, hair loss, and, in rare cases, pulmonary or neurological complications [9].

2. Variability in Patient Response to RA Treatments

What proves effective for one individual may offer minimal or no relief for another. While some patients experience significant improvement, others report only partial benefits or see the effects diminish over time. In particularly resistant cases, symptoms like pain, stiffness, and fatigue persist despite multiple treatment attempts, gradually eroding the quality of life and impacting daily activities, work, and personal relationships [10].

3. Current Therapies Focus on Symptom Management, Not Cure

There is currently no medication that can completely eliminate rheumatoid arthritis. Even when treatment is initiated early, it cannot reverse existing joint damage. Physicians often emphasize a critical early intervention window during which treatment may be most effective, but even within this period, achieving full disease control or a permanent cure remains unlikely [11].

4. Challenges in Long-Term Management of Rheumatoid Arthritis

Identifying the most effective medication or combination often involves a process of trial and error, with frequent dose adjustments at follow-up visits. While achieving remission is a desirable goal, reducing or discontinuing treatment can lead to disease flare-ups. Therefore, ongoing monitoring and timely modifications to the treatment plan are essential for sustained disease control [12].

5. Quality of Life and Cost-of-Care Considerations in RA Management

The combination of medication side effects, frequent clinic visits, and routine lab tests can take a physical and emotional toll on patients. Additionally, the high cost of advanced therapies, particularly biologics, can place a significant financial burden, further compounding the challenges of living with a chronic and demanding disease like RA [12].

2. Ethnomedicinal Background of Rheumatoid Arthritis Treatment

2.1 Traditional Systems of Medicine (Ayurveda, Siddha, Unani, Folk)

For generations, people living with rheumatoid arthritis (RA) have sought comfort in age-old healing paths-Ayurveda, Siddha, Unani, and local folk remedies-when modern drugs fall short or spark troubling side effects. These traditions treat the person, not just the swollen joint, aiming to bring the whole body back into harmony.

In Ayurveda, RA is named amavata, a condition born of built-up toxins (ama) and imbalanced doshas, especially vata. Care is highly personal and includes herbal mixes, cleansing routines such as panchakarma, medicated oils, specific meals, and gentle daily habits. The aim is to quell inflammation, purge ama, boost digestion, and reset the body's inner clock. Clinical trials also back this up, reporting better joint motion, less pain, and improved life quality, all with few side effects and solid safety records [13][14].

Siddha, mainly followed in South India, walks a similar path, using plant and even mineral medicines to restore energy balance and tackle the roots of joint trouble.

Unani medicine, drawing on Greco-Arab thought, eases Waja-ul-mafasil, or joint pain, with herbal mixes, meal plans, and gentle exercises, all meant to bring the body's humours back into balance [15]. In many villages, folk cures are handed down like family recipes. These cures may be home-made pastes, warming oils, or slow-brewed teas, each mixed to match the patient's signs and what the land provides. Though unofficial, they grow from years of careful watching and talking.

Modern science is starting to notice such traditions. Trials and reviews now say that Ayurvedic methods and other local medicines can offer safe, real relief if trained hands guide their use. What makes them stand out is a wide-eyed approach that treats the whole person, weaving together movement, food, and the mind [16][17].

In short, Ayurveda, Siddha, Unani, and countless village remedies bring fresh, all-around choices to people with rheumatoid arthritis. Their patient-by-patient plans, now backed by rising evidence, can sit beside or even lighten standard treatments.

2.2 Commonly Used Medicinal Plants in RA Management

For generations, people with rheumatoid arthritis (RA) have turned to nature for relief, relying on time-tested medicinal plants to ease pain, soothe inflammation, and improve daily movement. What began as traditional healing rooted in Ayurveda, Chinese medicine, and local remedies is now increasingly supported by science.

As shown in Table 1, turmeric and ginger are widely used in polyherbal formulations. Beyond their place in kitchens, they contain curcumin and gingerols compounds that naturally reduce inflammation and joint pain without many of the side effects linked to modern drugs [18][19]. In Chinese medicine, *Ligusticum chuanxiong* is another trusted herb, known for calming swollen joints through its bioactive compound ligustrazine, which can even slow joint damage when combined with standard therapies [20].

Table 1: Commonly Used Ethnomedicinal Plants in Polyherbal Formulations for RA

Plant Name (Botanical)	Common Name	Ethnomedicinal Use	Key Bioactive Compounds	Mechanism of Action
Zingiber officinale	Ginger	Used in Ayurveda for joint pain and inflammation	Gingerols, Shogaols	COX/LOX inhibition, antioxidant activity
Allium sativum	Garlic	Folk remedy for arthritis and inflammation	Allicin, Ajoene	Immunomodulatory, anti-inflammatory
Curcuma longa	Turmeric	Widely used for its anti-inflammatory properties	Curcumin	NF-κB inhibition, antioxidant
Vitex negundo	Nirgundi	Traditional analgesic and anti-inflammatory agent	Flavonoids, Iridoids	Reduces cytokine levels, modulates immunity
Rubia cordifolia	Indian Madder	Used in traditional medicine for joint disorders	Anthraquinones, Tannins	Free radical scavenging, anti-inflammatory

Some herbs, like *Aconitum kusnezoffii*, have potent pain-relieving properties but come with a caution that must be used carefully due to their toxicity, underscoring the need for medical supervision [20]. Meanwhile, *Paeonia lactiflora* (white peony) has gained formal recognition in China as a disease-modifying treatment, thanks to its inflammation-fighting extract called TGP [20].

Blended formulations like Wutou decoction combine several herbs to target different aspects of RA, offering a more comprehensive and balanced approach to treatment [19][20].

What sets these plants apart is their multi-targeted action; they not only calm inflammation but also help regulate the immune system, protect joints, and neutralize oxidative stress [19][21]. Backed by tradition and science, they are emerging as trusted natural allies in holistic RA management.

2.3 Ethnobotanical Approaches in Traditional Rheumatoid Arthritis Management

For countless generations, people battling rheumatoid arthritis (RA) have found comfort and relief in the healing power of medicinal plants. Rooted in age-old systems like Ayurveda, traditional Chinese medicine, and folk traditions, these natural remedies have stood the test of time. Today, science is finally catching up, uncovering how these plants ease inflammation, regulate immune responses, and support joint health.

Common kitchen spices like turmeric and ginger aren't just flavor enhancers, they're medicinal powerhouses. Compounds like curcumin and gingerols help reduce joint swelling and pain, often with fewer side effects than conventional treatments [22][23]. From traditional Chinese medicine, Ligusticum chuanxiong is known for easing joint inflammation, with its key component, ligustrazine, shown to lower inflammation markers and slow joint damage when used with standard RA drugs [24].

Another herb, Aconitum kusnezoffii, is known for its strong pain-relieving and anti-inflammatory properties. However, due to its potential toxicity, it should only be used under medical guidance [24]. White peony (Paeonia lactiflora) is another standout; its extract, TGP, has proven effective in reducing RA symptoms and is officially recognized in China as a disease-modifying therapy [24].

Herbal blends like the Wutou decoction combine several plants such as peony, ephedra, and astragalus for a more rounded and synergistic effect [23][24]. These remedies offer more than just symptom relief; they target inflammation, strengthen immunity, protect joints, and combat oxidative stress [24][25]. Altogether, these plants represent a bridge between ancient healing and modern medicine, offering promising natural options for managing RA safely and effectively.

2.3 Medicinal Plants from Northeast India and Other Biodiversity-Rich Regions

Rheumatoid arthritis (RA) is a chronic autoimmune disease that brings persistent joint pain and inflammation.

While modern medicine provides effective treatments, many people—especially in culturally rich and ecologically diverse regions like Northeast India continue to turn to traditional plant-based remedies for relief. This region, nestled within the Himalayan and Indo-Burma biodiversity hotspots, is home to indigenous communities whose deep knowledge of healing herbs has been passed down for generations [26].

Recent ethnobotanical studies have brought attention to several local plants commonly used to ease RA symptoms like swelling and stiffness. Among these are *Ageratum conyzoides, Centella asiatica, Clerodendron colebrookianum, Houttuynia cordata, Oroxylum indicum, Spilanthes paniculata, Paederia foetida, Psidium guajava,* and *Zingiber officinale*. These plants are typically prepared as herbal pastes, teas, or decoctions, and many are already showing promising results in scientific studies for their anti-inflammatory and healing properties [27].

What makes traditional healing in Northeast India so special is the way it reflects a deep connection between people and their natural surroundings. Different tribal groups across the region often use the same plants in unique ways, showing the richness of shared wisdom and local innovation. As researchers continue to explore these time-honored practices, they are uncovering natural remedies that could inspire new, safer treatments for RA while also emphasizing the importance of preserving both biodiversity and the cultural knowledge that thrives alongside it [28].

2.4 Bioactive Compounds in Major Herbs Used in Polyherbal Formulations

Polyherbal formulations are emerging as a gentle yet powerful approach to managing rheumatoid arthritis (RA), thanks to the natural synergy of their bioactive compounds. When herbs like ginger, garlic, clove, and eucalyptus are combined, they don't just bring individual benefits; they work together to tackle joint pain, swelling, and inflammation more effectively [29].

Each of these herbs offers something special: ginger provides gingerols, garlic contributes sulfur-rich compounds, clove adds eugenol, and eucalyptus offers 1, 8-cineole, all known for their strong anti-inflammatory and antioxidant actions. When blended into topical gels, these compounds create a synergistic effect that enhances relief while minimizing side effects often seen with conventional drugs [30][31].

Studies using experimental models of arthritis have shown that such formulations can reduce joint swelling and improve inflammatory markers in the blood. This is largely due to the presence of key phytochemicals like flavonoids, terpenes, alkaloids, and phenolics, which act on multiple fronts, calming oxidative stress, modulating immune response, and protecting joint tissues [31][32].

These findings not only validate traditional herbal wisdom but also open the door to integrating polyherbal remedies into modern RA care as safe, holistic options for long-term relief and better quality of life [27][32].

2.5 Synergistic Interactions in Polyherbal Combinations

Polyherbal formulations bring together the strengths of multiple medicinal plants to create a powerful, synergistic effect, something especially valuable in treating complex conditions like rheumatoid arthritis (RA). Instead of relying on a single remedy, these combinations allow different herbs to work in harmony, each contributing unique bioactive compounds that target various aspects of inflammation and oxidative stress [30][31].

Take ginger, garlic, clove, and eucalyptus, for example. Gingerols from ginger and eugenol from clove are both known to reduce inflammation, but when used together, they amplify each other's pain-relieving and anti-swelling effects. Garlic adds another layer of defense with its sulfur-based compounds that suppress key inflammatory signals, while eucalyptus oil helps calm the immune system by reducing cytokine levels [31][32].

This team-based approach not only makes these formulations more effective but also safer. Research shows that polyherbal gels and oils perform well in experimental models of arthritis, often matching or surpassing conventional treatments, but with fewer side effects. By acting on multiple pathways at once, these herbal blends offer a balanced, well-rounded strategy for managing RA, and reflect the growing scientific support for traditional remedies in modern healthcare [31][32].

2.6 Antioxidant, Anti-inflammatory, and Immunomodulatory Phytoconstituents

Polyherbal formulations are gaining recognition as a gentle yet powerful option for managing rheumatoid arthritis (RA), largely due to the rich mix of healing compounds found in herbs like ginger, garlic, clove, and eucalyptus. These plants are packed with natural substances like gingerols, sulfur compounds, eugenol, and 1,8-cineole that work together to tackle the root causes of RA [33][34].

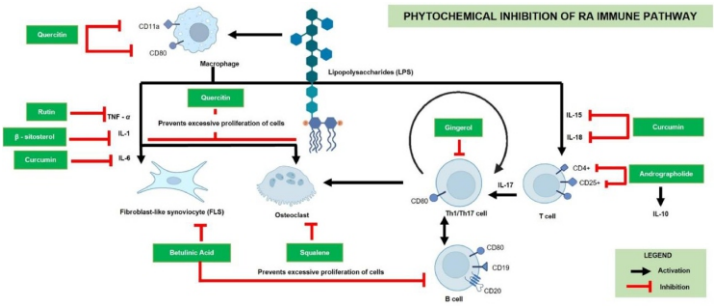

Figure 1. Mechanisms of phytochemicals in inhibiting key cytokines and cellular pathways involved in RA [33]

As shown in Figure 1, phytochemicals like quercetin, squalene, curcumin, and betulinic acid help ease joint inflammation by regulating immune cells and reducing pro-inflammatory cytokines such as TNF-α and IL-6. They also inhibit the growth of fibroblast-like synoviocytes and osteoclasts, protecting cartilage and bone from damage in rheumatoid arthritis.

One of their key strengths is fighting oxidative stress, which plays a major role in joint damage. These herbal compounds help neutralize harmful free radicals, protecting tissues from further harm. At the same time, they reduce inflammation by blocking key molecules like NF-κB and inflammatory cytokines that drive pain and swelling in RA [34].

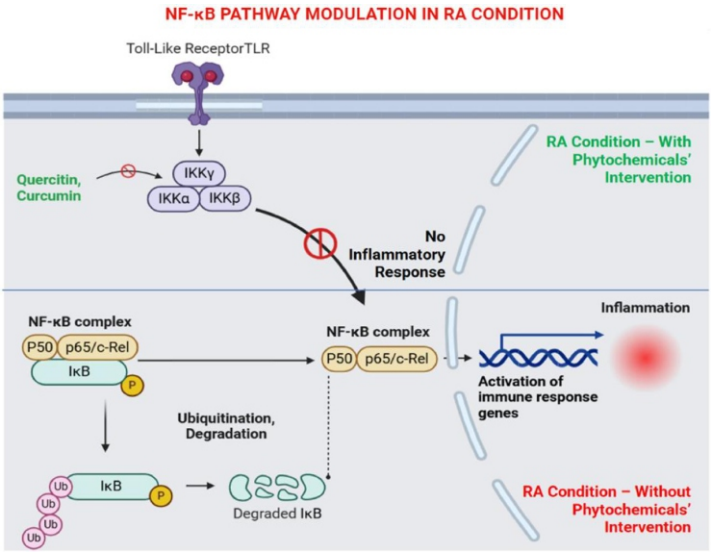

Figure 2. Role of Quercetin and Curcumin in inhibiting the NF-κB pathway to prevent inflammation in RA [33]

Figure 2 illustrates how curcumin and quercetin help control inflammation in RA by blocking the NF-κB pathway. Normally, this pathway gets triggered and drives inflammation, but these phytochemicals stop a key step, keeping NF-κB inactive in the cell cytoplasm and reducing the expression of genes that cause joint inflammation.

But their benefits don't stop there. These phytochemicals also help bring balance to the immune system, which is often overactive in people with RA. Garlic and eucalyptus, for instance, can lower pro-inflammatory signals while promoting better immune regulation.

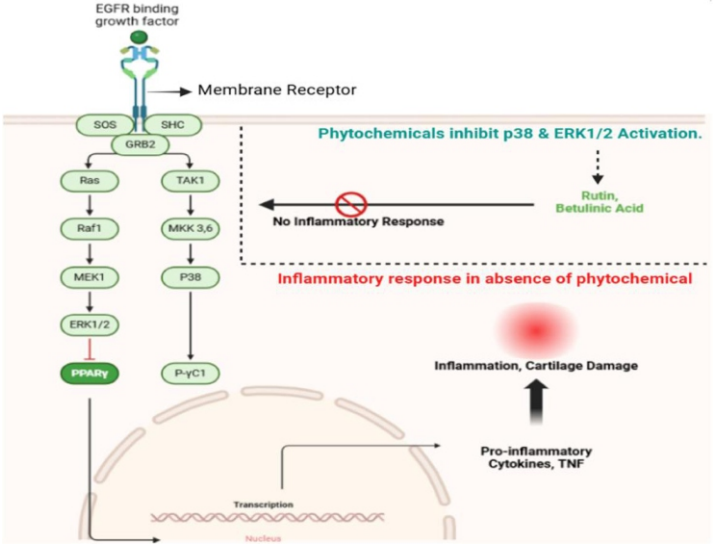

Figure 3. Inhibitory role of rutin and betulinic acid in suppressing EGFR-mediated inflammatory pathways to prevent cartilage damage [33]

Figure 3 highlights how the EGFR signaling pathway contributes to inflammation and cartilage damage in RA. When EGFR is activated, it sets off a chain reaction that blocks PPARγ a key regulator of inflammation leading to the overproduction of pro-inflammatory cytokines like TNF-α and IL-1β. This drives cartilage breakdown. The pathway also involves TAK1, which activates p38 MAPK and further fuels inflammation.

Rutin helps by boosting PPARγ activity, reducing cytokine levels and oxidative stress, while Betulinic Acid blocks key signaling steps, protecting cartilage [34][35].

Together, these antioxidant, anti-inflammatory, and immunomodulatory effects create a well-rounded, natural approach to RA care. As a complement to modern therapies, polyherbal formulations offer not just symptom relief, but also the promise of fewer side effects—making them a valuable option for long-term, holistic treatment [35][36].

3. Pharmacological Insights into Polyherbal Formulations

3.1 *In Vitro* and *In Vivo* Studies on Anti-RA Effects

Polyherbal formulations have gained considerable attention as promising therapeutic agents in the management of rheumatoid arthritis (RA), owing to their multifaceted pharmacological actions and favorable safety profile. A growing body of ***in vitro*** and ***in vivo*** evidence supports their anti-arthritic potential, highlighting their ability to modulate key inflammatory and immune pathways involved in RA pathogenesis [37]. Recent research is shedding fresh light on how polyherbal formulations can help manage rheumatoid arthritis (RA), and the results are encouraging. These multi-herb blends are emerging as safer, more holistic treatment options, especially when compared to conventional drugs. Both lab-based (in vitro) and animal (in vivo) studies have consistently shown that these combinations of medicinal plants can reduce joint inflammation, swelling, and other painful symptoms associated with RA [38].

For instance, topical gels prepared using extracts from ginger, garlic, clove, and eucalyptus have demonstrated powerful anti-inflammatory effects in animal models. Remarkably, their effectiveness often rivals that of standard non-steroidal anti-inflammatory drugs (NSAIDs), but without many of the usual side effects.

What makes these formulations stand out is the synergistic action of their key bioactive compounds like gingerols, sulfur-containing molecules, eugenol, and 1,8-cineole. Working together, these phytochemicals target multiple inflammatory pathways and help modulate immune responses, both critical in controlling RA progression [39].

Animal studies further support their benefits, showing improvements in blood health indicators and significant reductions in inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), both commonly elevated in active RA. Meanwhile, in vitro tests highlight strong antioxidant and anti-inflammatory properties, including the ability to prevent protein denaturation and suppress the release of harmful cytokines.

Altogether, these findings suggest that polyherbal therapies offer a well-rounded and body-friendly approach to RA management, relieving symptoms through multiple mechanisms while being kinder to the system than many conventional medications [40].

3.2 Molecular mechanism of anti-inflammatory action

Polyherbal formulations are emerging as powerful allies in the fight against rheumatoid arthritis (RA), thanks to their unique ability to combine the healing properties of multiple medicinal herbs. Unlike single-drug therapies that often target just one pathway, these natural blends work on several fronts, offering a more balanced and holistic approach to managing this complex autoimmune disease [44].

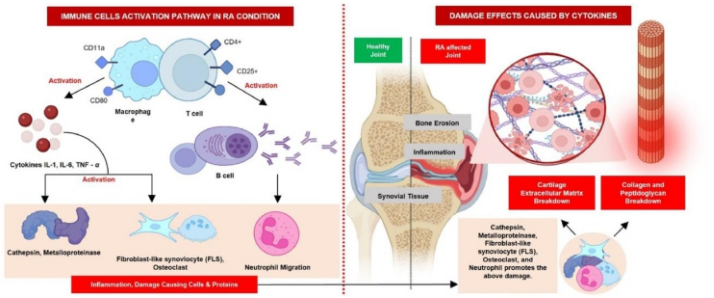

Figure 4. Cytokines' role in RA pathogenesis. The figure depicts the nature and mechanism of RA pathology, where pro-inflammatory cytokines [IL-1, IL-6, TNF-α] released after macrophage and T-cell activation activate fibroblast-like synoviocytes and osteoclasts [33].

Tumor necrosis factor-alpha (TNF-α) is a key inflammatory molecule in rheumatoid arthritis (RA), released by immune cells like macrophages and Th1 cells. It triggers inflammation, activates joint-lining fibroblasts, and contributes to tissue overgrowth and joint damage. TNF-α also stimulates enzymes that break down cartilage and bone, worsening joint erosion. Osteoclasts, the cells responsible for bone resorption, are activated during this process and further drive joint destruction. Similarly, interleukin-1β (IL-1β) levels are elevated in RA patients, contributing to inflammation and cartilage damage. Together, these cytokines play a central role in RA progression and joint deterioration [Figure 4].

The real strength of polyherbal therapies lies in their synergy. When herbs like ginger, garlic, and clove are used together, their active compounds such as gingerols, sulfur-containing molecules, and eugenol don't just add up their benefits; they amplify each other's effects. This happens in two ways [44, 45]:

- **Pharmacodynamic synergy**, where the compounds act on shared biological targets like COX and LOX enzymes, helps reduce the levels of inflammatory molecules such as TNF-α and interleukin-1β.

- **Pharmacokinetic synergy**, where one herb helps another get absorbed better or work more effectively, increasing the overall bioavailability and potency of the treatment.

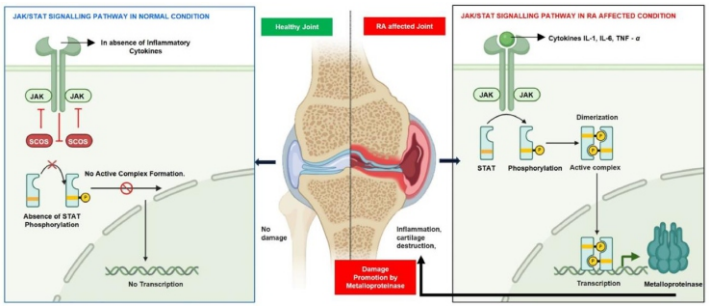

Figure 5. JAK/STAT signaling pathway modulation in RA condition, which shows the pathway is triggered by pro-inflammatory cytokines, leading to inflammation and synovial tissue repair

In rheumatoid arthritis (RA), several key molecular pathways drive joint damage and chronic inflammation. The p38 MAPK pathway responds to stress and inflammatory signals like TNF and IL-1, triggering enzymes and cytokines that cause cartilage and bone breakdown [Figure 5]. COX-2 promotes abnormal blood vessel growth in joints, feeding ongoing inflammation. MMP-9, a matrix-degrading enzyme, breaks down cartilage and activates other enzymes that worsen joint damage. JAK3, part of the JAK-STAT pathway, becomes overactive in RA due to faulty regulation, leading to the expression of genes that fuel inflammation and tissue destruction. Together, these molecules are central to RA progression.

Together, these mechanisms help reduce chronic inflammation, combat oxidative stress, and rebalance the overactive immune system, key issues at the heart of RA. Research has shown that polyherbal formulations can lower inflammation markers, improve joint health, and even down regulate genes linked to disease progression, with fewer side effects than many conventional drugs.

What makes these formulations especially promising is their ability to address multiple disease mechanisms simultaneously. Rooted in centuries of traditional medicine and now supported by modern science, polyherbal blends are proving to be not only effective but also safer options for long-term RA management. They represent a thoughtful integration of nature and evidence, offering new hope for those seeking gentler, yet effective, chronic care [41].

3.3 Pain and Joint Protection Mechanisms

Polyherbal formulations are emerging as a gentle yet effective way to manage rheumatoid arthritis (RA), offering relief from pain while also protecting the joints from long-term damage. By combining herbs like ginger, garlic, and clove, each rich in powerful natural compounds blends go beyond surface-level symptom relief to address the deeper causes of inflammation and joint deterioration [39][41].

One of the key ways these formulations work is by blocking enzymes like COX and LOX, which are responsible for producing inflammatory chemicals that cause pain and swelling. By interrupting these pathways, polyherbal blends can help reduce joint stiffness and discomfort at the root [40][41].

But their benefits don't stop there. These herbal combinations also reduce oxidative stress and help calm the overactive immune response that drives joint destruction in RA. This means they not only ease symptoms but also slow cartilage breakdown and protect joint structure over time.

Animal studies have supported these effects, showing improved mobility, reduced joint damage, and slower disease progression. What makes polyherbal formulations stand out is their ability to tackle multiple aspects of RA at once with fewer side effects than many conventional treatments [41].

As more research continues to back their effectiveness, these natural blends are becoming a trusted and holistic part of long-term RA care, offering pain relief with the added benefit of joint protection.

4. Formulation Approaches and Dosage Forms

4.1 Traditional vs. Modern Dosage Forms (e.g., decoctions, tablets, nanoformulations)

The way we use herbal remedies to manage rheumatoid arthritis (RA) has come a long way from simmering roots and leaves into decoctions to developing advanced pharmaceutical formulations. Traditionally, herbs like *Rubia cordifolia* and *Vitex negundo* were brewed into teas or pastes to draw out their anti-inflammatory benefits. While effective to some degree, these preparations often lacked consistency in strength and struggled with poor water solubility, making them less reliable for long-term treatment [42].

Today, modern science is breathing new life into these age-old remedies. Advanced delivery systems are helping to overcome traditional limitations and improve how these herbs work in the body. For example, polyherbal emulgels gels infused with oil-soluble herbal extracts have been developed for topical use. These offer better skin absorption and sustained drug release, providing pain relief for up to 8 hours, ideal for people with aching joints [43].

On the oral front, nanoformulations are proving to be game changers. Take curcumin, for instance: when delivered in lipid nanoparticles, its absorption can increase by 40 times compared to its raw form. This means more effective treatment at lower doses and with fewer side effects, especially compared to conventional drugs like NSAIDs, which can upset the stomach [37].

Even more exciting are hybrid delivery systems, like nanoemulsions combining *Piper nigrum* and *Myristica fragrans*, which not only provide sustained drug release (over 91%) but also significantly reduce key inflammation drivers like COX-2 and NF-kβ. In tablet form, standardized 500 mg polyherbal blends have shown results comparable to common anti-inflammatory drugs like indomethacin, cutting down paw swelling by up to 72% in lab models.

All of this reflects a promising shift: blending the wisdom of traditional medicine with the precision of modern drug delivery. It's a step toward developing safer, more effective, and culturally rooted treatments for RA that honor the past while embracing the future [44].

4.2 Biocompatible Carriers and Adjuvants in Polyherbal Drug Delivery

Polyherbal therapies for rheumatoid arthritis (RA) are getting a modern upgrade thanks to the use of adjuvants and biocompatible carriers that make them more effective and user-friendly. While traditional herbal remedies like decoctions and powders have long been valued in many cultures, they often came with drawbacks such as low absorption and inconsistent dosing [42][44].

Today, researchers are solving these issues by pairing herbal blends with smart delivery systems. Adjuvants are added to enhance the therapeutic effects, while advanced carriers like hydrogels and emulgels help stabilize the active compounds, release them in a controlled manner, and improve absorption through the skin.

One standout example is a carbopol-based emulgel containing hydroalcoholic extracts of *Rubia cordifolia, Vitex negundo, Piper nigrum,* and *Myristica fragrans*. This formulation delivered over 91% of its active ingredients within 8 hours and showed strong anti-arthritic effects in lab tests and revealing the powerful combination of herbal synergy and a well-designed delivery system.

Topical gels made with familiar herbs like ginger, garlic, clove, and eucalyptus oil are also proving their worth. These formulations not only reduce inflammation and pain more effectively than traditional remedies, but they're also easier to use and gentler on the body, improving patient comfort and compliance [44].

Together, these innovations show how blending traditional herbal wisdom with modern pharmaceutical tools is creating safer, more effective, and more convenient treatment options for people living with RA.

5. Standardization and Quality Control Challenges

Ensuring consistent quality and efficacy in polyherbal formulations for rheumatoid arthritis remains a major challenge. Unlike synthetic drugs, herbal products are inherently complex, with their therapeutic potential influenced by factors such as plant species, harvesting time, and extraction methods. These variables can cause significant batch-to-batch differences, making it difficult to maintain uniform potency and safety.

For example, even slight variations in how herbs like *Rubia cordifolia* or *Vitex negundo* are sourced or processed can alter their anti-inflammatory properties, complicating both clinical effectiveness and regulatory approval [41].

To tackle this, modern formulation efforts are turning to advanced analytical tools like high-performance liquid chromatography (HPLC), which allow precise fingerprinting and quantification of active phytochemicals. However, consistency becomes even more difficult when multiple herbs are combined in a single formulation, and the absence of universal standards for polyherbal products further complicates quality control.

Experts are increasingly calling for strict standardization protocols and the adoption of Good Manufacturing Practices (GMP) to ensure product reliability. These steps are essential not only for gaining regulatory trust but also for ensuring that polyherbal remedies for rheumatoid arthritis are safe, effective, and reproducible for long-term therapeutic use [44].

6. Preclinical and Clinical Evaluations

6.1 Preclinical Toxicity and Efficacy Studies

Before polyherbal formulations can be considered for treating rheumatoid arthritis (RA) in humans, they must go through a series of preclinical studies to assess both their safety and effectiveness. These studies often use well-established animal models, such as adjuvant-induced arthritis in rats, which closely mimic the joint inflammation and damage seen in human RA. Through these models, researchers can evaluate whether specific herbal combinations like those containing *Rubia cordifolia*, *Vitex negundo*, and *Piper nigrum* can reduce joint swelling, regulate inflammatory markers such as TNF-α, and help protect cartilage from further deterioration [38].

Safety is just as important as efficacy. That's why toxicity studies, including acute and sub-chronic evaluations, are carried out to detect any potential harm to vital organs or general health. Encouragingly, most well-designed polyherbal formulations show minimal to no signs of liver or kidney toxicity at recommended doses, supporting their overall safety [42].

The effectiveness of these herbal blends is gauged through indicators like reduced paw swelling, balanced blood cell counts, and healthier joint tissue on microscopic analysis. In fact, some formulations have demonstrated anti-arthritic effects comparable to standard drugs like indomethacin, achieving up to 72% reduction in inflammation and effectively targeting key enzymes like COX and LOX involved in the inflammatory process [43].

As shown in Table 2, all these findings from preclinical research provide a solid foundation for moving forward with clinical trials, offering hope that these plant-based remedies could emerge as safe, effective, and natural alternatives for managing rheumatoid arthritis [44].

Table 2: Pre-clinical Studies on Polyherbal Formulations for RA

Formulation Components	Animal Model	Outcome Measures	Results
Glycosmis pentaphylla, *Tridax procumbens*, *Mangifera indica*	Adjuvant-Induced Arthritis (AIA) in rats	Paw edema, hematological parameters	Comparable to indomethacin, a significant reduction in inflammation
Zingiber officinale, *Allium sativum*, *Syzygium aromaticum*	CFA-induced arthritis	Cytokine profiling, joint histology	Decreased TNF-α, IL-6; improved joint integrity
Andrographis paniculata, *Nardostachys jatamansi*, *Celastrus paniculatus*	In vitro and in vivo inflammation models	NO inhibition, COX-2 suppression	Greater efficacy than diclofenac gel

6.2 Clinical Trials of Polyherbal Formulations in RA Patients

Clinical trials investigating polyherbal remedies for rheumatoid arthritis (RA) are painting an encouraging picture, though not without a few challenges. Studies involving herbal blends such as *Tripterygium wilfordii*, *Paeonia lactiflora*, and *Olea europaea* (olive) have shown that these formulations, whether taken on their own or alongside standard medications, can ease joint pain, improve mobility, reduce inflammation, and lower disease activity scores. Even common ingredients like garlic (*Allium sativum*) and rosehip (*Rosa canina*), when used in powdered form, have helped patients feel less pain and move more freely, all while reporting minimal side effects [44][45].

But despite these positive outcomes, there's still work to be done. Many of the studies conducted so far have involved small groups of participants and lacked the rigorous designs needed to draw firm conclusions. The complexity of polyherbal formulations often containing dozens of active plant compounds also makes it tricky to pinpoint exactly which ingredients are doing the heavy lifting. Topical gels made from herbs like ginger, garlic, clove, and eucalyptus have shown early promise in reducing inflammation and discomfort, but these too need further testing in larger, well-structured clinical trials [Table 3].

In short, polyherbal formulations show a lot of promise as complementary treatments for RA. Their broad-spectrum benefits and generally safe profiles make them appealing options. Still, more high-quality, large-scale research is essential to confidently integrate these natural remedies into mainstream RA management [44][45].

Table 3: Clinical Trials on Polyherbal Formulations in RA

Formulation Name/Plants	Study Design	Sample Size	Outcomes	Findings
Tripterygium wilfordii, *Paeonia lactiflora*	Randomized, controlled trial	120 RA patients	DAS28 score, ESR, CRP levels	Significant improvement vs placebo
Allium sativum, *Rosa canina*	Open-label clinical trial	45 RA patients	Pain score, stiffness, mobility	Reduced pain, improved function
Ginger, *Garlic*, *Clove*, *Eucalyptus* gel	Double-blind, topical application	60 RA patients	Pain relief, swelling reduction	Comparable to diclofenac gel, better tolerability

6.3 Comparative Efficacy with Synthetic DMARDs and NSAIDs

When comparing polyherbal formulations with conventional rheumatoid arthritis (RA) medications like DMARDs and NSAIDs, the results are both promising and thought-provoking. In preclinical studies, certain herbal combinations such as *Glycosmis pentaphylla*, *Tridax procumbens*, and *Mangifera indica* have shown anti-arthritic effects similar to standard drugs like indomethacin. These herbal blends have effectively reduced inflammation and improved blood markers in animal models of arthritis. Topical emulgels containing herbs like *Nardostachys jatamansi*, *Andrographis paniculata*, and *Celastrus paniculatus* have even outperformed commonly used diclofenac gel in lab tests and animal studies, showing stronger anti-inflammatory activity [40][42].

Clinically, patients using polyherbal formulations, especially in combination with conventional treatments, have reported better disease control, lower inflammation levels, and overall improvement in symptoms. Many also experience fewer side effects compared to synthetic drugs, which are often linked to gastrointestinal discomfort or immune system issues. This makes polyherbal therapies an appealing option, particularly for those seeking gentler or more natural approaches [41][43].

That said, while the benefits are encouraging, current evidence suggests that these plant-based formulations are best used as complementary therapies rather than replacements for conventional treatments. Their full therapeutic potential still needs confirmation through large, high-quality clinical trials [45].

In summary, polyherbal formulations offer a promising and safer addition to traditional RA treatment plans. They may be especially valuable for patients looking for holistic or low side effect options, but ongoing research is key to defining their place in long-term RA care.

6.4 Safety and Tolerability

Polyherbal formulations have shown a strong safety and tolerability profile in both animal and human studies for managing rheumatoid arthritis. Herbal blends like *Glycosmis pentaphylla*, *Tridax procumbens*, and *Mangifera indica* demonstrated powerful anti-arthritic effects without causing toxicity, even at high doses [53][54]. Topical gels made with ginger, garlic, clove, and eucalyptus also proved safe and effective in reducing inflammation and pain. Clinical studies, such as those involving Qurs-e-Mafasil, showed comparable results to NSAIDs like celecoxib, but with fewer side effects. Overall, polyherbal therapies are well-tolerated and offer a safer, natural alternative or complement to conventional RA treatments [56][60].

7. Standardization and Authentication of Raw Materials

Developing polyherbal formulations for rheumatoid arthritis comes with a unique set of challenges, especially when it comes to ensuring the quality and consistency of raw plant materials. Unlike synthetic drugs, which have a single active ingredient, polyherbal products combine multiple plant extracts, each with its own complex mix of bioactive compounds. Variations in plant species, harvest times, and processing methods can significantly impact both the safety and effectiveness of the final product [44] [45].

A major hurdle is the lack of universally accepted quality standards for herbal medicines. While regulatory systems like India's Drugs and Cosmetics Act provide some guidelines, enforcement is often inconsistent. This can lead to unreliable products reaching the market, affecting both clinical outcomes and public trust [45].

To improve quality, researchers are turning to advanced techniques like HPLC and mass spectrometry to verify and standardize herbal components. However, creating consistent, validated protocols for extraction and characterization across different formulations remains an ongoing effort [45].

7.1 Regulatory Guidelines in Herbal Drug Development (Humanized, 200 words)

As interest in herbal medicines continues to grow, regulatory systems worldwide are working to create more consistent guidelines to ensure the safety and effectiveness of polyherbal therapies. In the European Union, the Committee on Herbal Medicinal Products (HMPC) helps set the standard by publishing herbal monographs, detailed documents that guide the approval of traditional and well-established herbal products. These monographs aim to make sure that only high-quality, well-researched herbal medicines reach the public [62].

The World Health Organization (WHO) has also taken a lead role by issuing updated 2025 guidelines. These global recommendations cover everything from labeling and standardization to Good Manufacturing Practices (GMP), helping bring traditional remedies in line with modern safety standards [63].

In the U.S., the FDA's "Botanical Drug Development" guideline outlines a rigorous process for approving herbal drugs, requiring strong evidence of quality, safety, and clinical effectiveness through the IND and NDA pathways [63] [64].

Still, challenges remain. Many regions struggle with inconsistent quality control, incomplete phytochemical profiling, and gaps in regulatory enforcement. To overcome these hurdles, better collaboration is needed among global regulators, scientists, and traditional healers [64].

Strengthening these regulatory frameworks is key to making polyherbal formulations a trusted, credible part of mainstream healthcare, especially for chronic conditions like rheumatoid arthritis.

7.2 Marketed Polyherbal Formulations for RA (Indian and Global)

Polyherbal formulations for rheumatoid arthritis (RA) have made their way into the market by blending age-old herbal wisdom with modern pharmaceutical advancements [Table 4]. In India, widely used products like Artha Cure oil and Arthcure capsules feature powerful medicinal plants such as *Syzygium aromaticum* (clove), *Allium sativum* (garlic), *Zingiber officinale* (ginger), and *Aloe vera,* all known for their anti-inflammatory and pain-relieving properties [46] [47]. These remedies are manufactured using up-to-date technologies to ensure quality and are offered in convenient forms like oils, capsules, and gels, making them easier for patients to use regularly.

On the global front, traditional systems like Chinese and Unani medicine offer similar polyherbal options. Formulations such as Tongbiling (TBL-II) and HLXL are under scientific investigation for their effectiveness against arthritis, showing encouraging results in both laboratory and clinical settings. Topical gels combining herbs like ginger, garlic, clove, and eucalyptus are also gaining popularity for providing targeted pain relief with fewer side effects compared to conventional NSAIDs [47] [48].

The growing use of these products reflects a shift toward more holistic treatment approaches. Still, their long-term acceptance will depend on maintaining strict quality standards, ensuring consistency, and backing claims with solid clinical research, key steps for integrating polyherbal therapies into modern RA care [48].

Table 4: Marketed Polyherbal Formulations for RA in India

Product Name	Manufacturer	Key Ingredients	Dosage Form	Claimed Benefits
Arthcure Capsules	Ayurvedic Research Center	Aloe vera, Colchicum luteum, Piper longum, Zingiber officinale	Capsule	Reduces inflammation, pain, improves mobility
Artha Cure Oil	Multani Pharmaceuticals	Syzygium aromaticum, Aconitum ferox, Myristica fragrans	Topical Oil	Relief from joint pain, stiffness
Qurs-e-Mafasil	Hamdard	Unani herbs, including *Colchicum*, *Withania somnifera*	Tablet	Antiarthritic, muscle relaxant

7.3 Limitations and Quality Assurance [49]

(i) Synergistic Benefits with Complexity

Polyherbal formulations offer enhanced therapeutic effects by combining multiple herbs, but this complexity also increases the risk of chemical incompatibilities that can affect product stability and safety.

(ii) Inconsistent Raw Material Quality

Differences in plant species, growing conditions, harvest seasons, and extraction methods can lead to inconsistent efficacy across different batches of the same formulation.

(iii) Regulatory Gaps

Lack of universally enforced quality standards, especially in regions using traditional medicine systems like Ayurveda, makes it difficult to guarantee product consistency and safety.

(iv) Need for Advanced Quality Control

Techniques like phytochemical fingerprinting, chromatography, and spectrometry are essential tools for ensuring the reproducibility and reliability of polyherbal blends.

(v) Path to Mainstream Acceptance

For polyherbal therapies to be widely accepted in modern medicine, rigorous standardization, strong regulatory oversight, and reliable quality assurance practices must be implemented consistently.

8. Future Perspectives and Research Opportunities

The future of polyherbal formulations for rheumatoid arthritis (RA) is bright, offering a promising fusion of traditional knowledge and modern science. Ethnopharmacology, rooted in centuries of traditional healing, serves as a valuable guide for identifying effective medicinal plants. When combined with advanced tools like high-throughput screening and bioassays, it opens the door to developing multi-target therapies tailored to RA's complex nature. While many herbs have already shown anti-inflammatory and immune-modulating potential, translating these benefits into clinical practice requires large-scale, well-designed human trials across diverse populations [50] [51].

Cutting-edge techniques like omics and network pharmacology are helping researchers understand how multiple plant compounds work together in the body, offering deeper insights into their mechanisms. Looking ahead, innovations such as improved drug delivery systems and refined formulations can boost both efficacy and patient convenience. With strong quality control, clear regulatory pathways, and a focus on patentable innovations, polyherbal therapies could soon become trusted, mainstream options in RA care [51] [52].

9. Conclusion

Polyherbal formulations are emerging as a powerful, nature-inspired approach to managing rheumatoid arthritis (RA). Rooted in traditional medicine and supported by modern research, these plant-based blends, often including herbs like ginger, garlic, clove, and eucalyptus, have shown encouraging results in easing joint pain, reducing inflammation, and modulating the immune system. Unlike many conventional drugs, they tend to have fewer side effects, making them especially appealing for patients seeking gentler, more holistic treatment options.

What sets these formulations apart is their synergistic action multiple plant compounds working together to enhance therapeutic effects while minimizing toxicity. This makes them valuable alternatives or add-ons for those who can't tolerate standard treatments like DMARDs or NSAIDs.

Still, their true potential can only be realized by addressing key challenges. Quality control, standardization, and clinical validation remain critical. Ensuring consistency from batch to batch, adhering to WHO and national guidelines, and conducting large-scale clinical trials are all essential next steps.

Looking ahead, integrating modern tools like omics technologies and network pharmacology can deepen our understanding of how these complex herbal combinations work. With innovation in formulation, delivery systems, and regulatory compliance, polyherbal therapies could soon take a well-deserved place in mainstream RA management offering safe, effective, and patient-friendly care.

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