







Review Article

Herbal Remedies as Adjunct Therapies for Rheumatoid **Arthritis: Focus on Ginger: A Review**

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Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disorder characterized by persistent joint inflammation, pain, and progressive disability. While conventional pharmacological treatments remain the cornerstone of RA management, growing interest in alternative and complementary therapies has drawn attention to the medicinal potential of natural compounds such as ginger (Zingiber officinale). This review investigates the therapeutic role of ginger in alleviating RA-related symptoms, with a particular focus on its anti-inflammatory and immunomodulatory mechanisms. Bioactive constituents such as gingerols and shogaols have demonstrated the ability to inhibit pro-inflammatory cytokines and oxidative stress pathways implicated in RA pathogenesis. Clinical and preclinical studies provide preliminary evidence supporting ginger's efficacy and safety. This paper highlights current findings and outlines future directions for integrating ginger as a complementary therapeutic option in RA management.

Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disorder in which the immune system mistakenly attacks the synovial lining of joints, leading to persistent inflammation, pain, and joint destruction. In severe cases, this process may result in irreversible joint damage, functional disability, and diminished quality of life [1]. Beyond the musculoskeletal system, RA can affect extra-articular organs, including the lungs, heart, skin, eyes, and vasculature [1,2]. The global prevalence of RA is approximately 0.5%, with women affected two to three times more frequently than men. Peak onset typically occurs between 50 and 59 years of age [1,3].

The pathogenesis of RA is multifactorial and remains incompletely understood, involving genetic predisposition, dysregulated environmental triggers, and responses [4]. Its heterogeneous clinical presentation and variable therapeutic responses highlight the complexity of the disease [4,5]. RA is associated with increased risks of serious infections, interstitial lung disease, cardiovascular complications, malignancies, osteoporosis, and premature mortality compared to the general population [3,5].

Nevertheless, early diagnosis and aggressive treatment particularly with disease-modifying antirheumatic drugs (DMARDs)—have significantly improved patient outcomes [3].

Clinically, RA often presents as symmetrical polyarthritis, primarily affecting the small joints of the hands, wrists, feet, and knees [1,6]. Morning stiffness lasting longer than 30 minutes, along with joint swelling, warmth, and tenderness, are hallmark symptoms [6]. In some cases, monoarthritis or oligoarthritis may precede more widespread involvement. Extra-articular manifestations, such as interstitial lung disease, pericarditis, and pleural effusion, may even occur without prominent joint symptoms [3]. Additional systemic symptoms include fatigue, low-grade fever, poor appetite, and unintended weight loss [6]. Despite advances in treatment, a subset of patients fails to achieve remission or low disease activity due to factors such as autoantibody positivity, joint erosion, genetic susceptibility, extra-articular involvement, or comorbid conditions [4,5].

The use of complementary and alternative medicine (CAM) has grown significantly among patients with chronic inflammatory conditions. In the United States, CAM utilization

rose from 34% in 1990 to over 42% in 1997, surpassing even the frequency of primary care visits [7]. Herbal medicine—one of the most widely used CAM modalities-relies on various plant parts, often used synergistically, under the belief that whole plant formulations offer a more balanced and sustained healing effect compared to isolated compounds [8]. Among these, ginger (Zingiber officinale) has emerged as a promising adjunctive therapy due to its well-documented anti-inflammatory and immunomodulatory properties [8-10]. This review explores the current evidence regarding ginger's potential role as an adjunct treatment for rheumatoid arthritis [11-15].

Pathophysiology of rheumatoid arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of the synovial joints, leading to cartilage degradation, bone erosion, and functional impairment [16]. The pathogenesis involves a complex interplay between genetic predisposition and environmental triggers, initiating an aberrant immune response [4,17]. At the cellular level, the disease is marked by the infiltration of immune cells-such as T lymphocytes, B cells, macrophages, and dendritic cells—into the synovial tissue. These cells produce pro-inflammatory cytokines, including tumor necrosis factoralpha (TNF- α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which drive the inflammatory cascade [18,19].

Additionally, the activation of nuclear factor-kappa B (NFкВ) and mitogen-activated protein kinases (MAPKs) further amplifies the inflammatory response [19,20]. The synovial lining becomes hyperplastic, forming pannus tissue that invades and destroys adjacent cartilage and bone. This process is facilitated by the release of matrix metalloproteinases (MMPs) and receptor activator of nuclear factor-kappa B ligand (RANKL), which promote osteoclastogenesis and subsequent bone resorption [19,21].

Systemic manifestations of RA include fatigue, anemia, and an increased risk of cardiovascular disease [3,16]. The chronic inflammation can also affect other organs, leading to complications such as rheumatoid nodules, interstitial lung disease, and vasculitis [3]. Understanding the pathophysiological mechanisms of RA is crucial for developing targeted therapies aimed at modulating the immune response and preventing joint damage [17].

Inactive compounds in ginger

Ginger (Zingiber officinale Roscoe) is a member of the Zingiberaceae family of plants. Some studies have proven that ginger is the most-used herbal drug in many countries [22]. Scientific evidence supports its antioxidant and antiinflammatory capacities; in contrast, a more specific and less-studied bioactivity is its possible neuroprotective effect [22,23]. Zingiber officinale is among the medicinal plants with beneficial health effects that have been widely used in both pharmaceutical products and food [8]. Its crude extract is known for its pharmacological effects, especially due to its bioactive phytochemicals [9,23].

Ginger rhizome is commonly added to food as a spice or taken as a dietary supplement, and has been widely used in traditional medicine across various cultures [8,24]. One of its main traditional uses includes treating urinary tract inflammatory problems [24]. Furthermore, its antiinflammatory properties, due to immune response modulation during the cellular phase, have been well described [23].

Another highlighted effect of ginger extract is its antinociceptive activity induced by acetic acid [25]. Its bioactive compounds (e.g., gingerols and shogaols) have analgesic and anti-inflammatory properties by inhibiting the COX-2 and LOX pathways, thereby preventing arachidonic acid metabolism [23,25]. The action of ginger has been shown to resemble that of NSAIDs, though notably, it does not damage the gastric mucosa [26].

The rhizome of Zingiber officinale is extensively used in medicinal applications. Ayurvedic literature highlights its use for both communicable and non-communicable diseases [24]. Modern studies in analytical chemistry, cytology, and microbiology support its application in various disease conditions. Ginger is reported to have antiviral, radioprotective, anticancer, antioxidant, and anti-inflammatory effects, aligning with its Ayurvedic profile [24].

It is also considered beneficial for boosting appetite, immunity, and reinvigorating weakened physiological systems. Active constituents such as 6-gingerol, 6-shogaol, 6-paradol, zingerone, and zerumbone are believed to promote enzyme activity, regulate circulation, and rejuvenate the body by restoring physical strength [24].

Anti-inflammatory and immunomodulatory effects of ginger

Zingiber officinale is highly effective in treating inflammation associated with the alimentary tract, including conditions such as colitis [27]. Ginger's bioactivity has been linked to its modulation of the phosphatidylinositol-3-kinase (PI3K)/ protein kinase B (Akt) pathway and the nuclear factor kappalight-chain-enhancer of activated B cells (NF-kB) signaling pathway [28,29]. In particular, 6-shogaol has demonstrated protective effects against TNF- α -induced dysfunction in human intestinal epithelial cell models [28].

Physiologically, ginger helps attenuate post-exercise inflammation by reducing the elevation of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α) [28,30]. In the context of inflammatory bowel disease (IBD), Z. officinale shows efficacy by suppressing pro-inflammatory cytokines and enhancing anti-inflammatory cytokine expression, largely due to its effect on the Akt/NF-KB axis [28].

Moreover, gingerols in Z. officinale exert anti-prostaglandin effects, which have been shown to reduce menstrual pain in patients with dysmenorrhea [31]. In addition to prostaglandins, ginger inhibits leukotriene biosynthesis by suppressing 5-lipoxygenase (5-LOX) activity [31]. The hexane fraction

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of ginger rhizome extract has also been found to inhibit the overproduction of nitric oxide (NO) and IL-1 β , especially in allergic reactions [32]. These findings suggest ginger is useful not only for symptom relief but also for the management and prevention of allergic diseases.

Notably, 6-shogaol is effective in managing gout, a rheumatic joint disease, due to its potent anti-inflammatory and urate-lowering activities [33]. Additionally, *Z. officinale* supports restoration of cardiac function, pain control, physical recovery, and appetite enhancement, aligning with both modern scientific findings and Ayurvedic medicine principles [24,33].

Clinical evidence supporting ginger in RA treatment

Recent studies have highlighted the therapeutic potential of ginger and its bioactive compounds in the management of rheumatoid arthritis (RA). In a randomized, double-blind clinical trial, Aryaeian, et al. [1] administered 1.5 grams of ginger powder daily for 12 weeks to 66 patients with active RA. The intervention group demonstrated a significant reduction in high-sensitivity C-reactive protein (hs-CRP) levels (p = 0.050) and IL-1p mRNA expression (p = 0.021) compared to the placebo group. TNF-patharpha mRNA expression also showed a downward trend (p = 0.093), indicating ginger's ability to modulate inflammatory biomarkers in human subjects [34].

In animal and *in vitro* models, Jo, et al. [21] investigated the effects of 8-shogaol, a potent ginger-derived compound, and found it significantly inhibited $TNF-\alpha$, $IL-1\beta$, and IL-17-mediated inflammation in 3D human synovial cultures. Furthermore, in a rat adjuvant-induced arthritis model, 8-shogaol treatment reduced paw swelling, improved walking performance, and reversed structural joint damage.

Similarly, a study by Zhu, et al. using the collagen-induced arthritis (CIA) mouse model revealed that intraperitoneal administration of 6-shogaol (30-60 mg/kg/day for 21 days) preserved cartilage integrity, reduced leukocyte infiltration, lowered VCAM-1 expression, and decreased joint swelling.

On a molecular level, both 6-gingerol and 8-shogaol have been shown to inhibit COX-2 and lipoxygenase (LOX) enzymes, reducing the synthesis of prostaglandins and leukotrienes. These compounds also suppress key inflammatory signaling pathways such as NF- κ B and MAPK/PI3K-Akt, leading to decreased expression of pro-inflammatory cytokines including IL-1 β , TNF- α , and IL-6.

Collectively, these findings provide compelling evidence that ginger and its active constituents possess anti-inflammatory and immunomodulatory properties, supporting their role as promising adjunct therapies in the treatment of RA.

Clinical evidence for ginger in RA (Table 1)

Safety, dosage, and limitations

Ginger is generally regarded as safe when consumed in moderate amounts, either as a dietary supplement or food

Table 1: Clinical Evidence for Ginger in RA.

Study (year)	Sample size	intervention	Dosage	Duration	Outcome
Aryaeian, et al. [1]	70 RA patients	Ginger powder vs. placebo	1,500 mg/ day	12 weeks	↓DAS-28 score,↓CRP, ↓IL-1β,↓TNF-α
Foshati, et al. [2]	66 RA patients	Ginger supplementation	1,200 mg/ day	12 weeks	Significant ↓ in disease activity and joint pain
Srivastava, et al. [4]	40 RA patients	Ginger extract capsule	750 mg/ day	8 weeks	Modest ↓ in joint stiffness and inflammatory markers
Long, et al. [17]	Systematic review	Multiple RA/OA studies	750– 2,000 mg/ day	2-12 weeks	Consistent ↓ in inflammatory markers and pain scores in RA

ingredient. According to the U.S. Food and Drug Administration (FDA), ginger is classified under the category of "Generally Recognized As Safe (GRAS)" substances. Most clinical studies investigating the medicinal use of ginger report minimal side effects, typically limited to gastrointestinal discomfort such as heartburn, bloating, and mild nausea.

The effective dose of ginger for anti-inflammatory purposes in RA has not yet been standardized. However, several studies have explored daily doses ranging from 500 mg to 2,000 mg of standardized ginger extract, often administered in divided doses. In a double-blind, placebo-controlled trial, Aryaeian, et al. [1] reported that 1,500 mg/day of ginger powder taken over 12 weeks significantly reduced inflammatory markers in RA patients without serious adverse effects [34].

Despite these promising results, several limitations remain. A major concern is the low bioavailability of ginger's active constituents, particularly gingerols and shogaols, which may reduce its *in vivo* therapeutic efficacy. Moreover, existing studies vary significantly in terms of design, sample size, dosage, and preparation method, making direct comparisons and clinical application difficult. Importantly, there is a lack of long-term safety data, particularly concerning potential interactions with conventional RA medications such as NSAIDs, corticosteroids, and biologic agents.

Therefore, it is crucial that patients consult healthcare providers before integrating ginger into their treatment regimen. Additionally, further large-scale, randomized controlled trials are essential to determine the optimal dosing, confirm long-term safety, assess combination therapy outcomes, and support the inclusion of ginger as a complementary therapy in RA management (Figure 1).

Dose-effect curve chart

Potential for herb-drug interactions

Ginger exhibits pharmacological activity that may pose interaction risks when taken concurrently with rheumatoid arthritis (RA) medications such as DMARDs or biologics. Its known antiplatelet effects can potentially increase the risk of bleeding, especially when combined with NSAIDs,



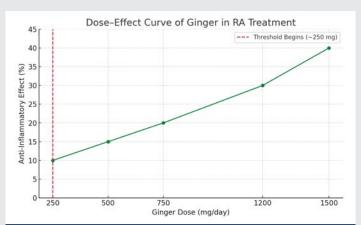


Figure 1: Dose-response relationship between ginger supplementation and antiinflammatory effect in RA patients, based on findings from Aryaeian, et al. [1], Foshati, et al. [2], Srivastava & Mustafa [4], and others.

corticosteroids, or anticoagulants like warfarin [4,5]. Additionally, ginger may modulate cytochrome P450 enzymes, which are involved in the metabolism of drugs like methotrexate, potentially altering therapeutic levels [5].

Moreover, as both ginger and DMARDs immunomodulatory effects, there is theoretical concern regarding synergistic or antagonistic immune modulation [6]. Although no severe adverse interactions have been reported in trials, caution is advised. Patients should consult with healthcare professionals before initiating ginger supplementation, especially those undergoing combination therapy for RA [6].

Conclusion and future directions

Ginger (Zingiber officinale) has demonstrated notable potential as a complementary therapy for managing rheumatoid arthritis (RA). Its bioactive constituents, primarily gingerols and shogaols, have shown anti-inflammatory, antioxidant, and immunomodulatory effects through the inhibition of proinflammatory cytokines such as TNF- α , IL-1 β , and IL-6 [18,19]. These properties align with the pathological mechanisms involved in RA, positioning ginger as a viable natural adjunct to conventional treatment.

While clinical trials have reported positive effects of ginger on joint pain and inflammatory markers in RA patients [11, 23], several gaps remain. Existing studies often vary in dosage, preparation form, and duration, and are generally limited by small sample sizes and short follow-up periods [22]. Moreover, concerns regarding the bioavailability of active compounds and the potential interactions with standard RA medications warrant further investigation [20].

- Future research should focus on the following directions:
- Conducting large-scale, randomized controlled trials with standardized ginger preparations to establish consistent dosage and treatment protocols [22].
- Exploring long-term safety and efficacy of ginger supplementation when combined with conventional RA treatments [20].

- Investigating the pharmacokinetics of gingerols and shogaols to enhance bioavailability and therapeutic outcomes [8].
- Studying the molecular mechanisms by which ginger modulates immune responses in autoimmune diseases such as RA [17,18].

By addressing these limitations, ginger could become an evidence-based, cost-effective, and accessible option in integrative RA care strategies.

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