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Anti-Inflammatory Effect of Ginger Ointment in Rheumatoid Arthritis: An Explanatory Review

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Abstract: The prevalence of rheumatoid arthritis (RA) in adults is 14.1% globally and 0.7% in India. Considerable progress has been achieved in the last twenty years about the etiology, prognosis, and therapeutic approaches of RA. In 90% of cases, early diagnosis and therapy can stop or lessen joint erosion, preventing permanent impairment. The prognosis for RA has improved because of advancements in therapeutic approaches and diagnostic technologies. Immuno-modulating antirheumatic drugs, nonsteroidal anti-inflammatory drugs, glucocorticoids, and potent biologically active medications such as bisphosphonate agents and monoclonal antibodies are used. In three months, target-treatment techniques seek to eliminate 50% of disease activity; in six months, they seek to reduce disease progression. The health-promoting features and perspective of ginger have been contributed by its phytochemistry as a beneficial herbal drug for centuries. The anti-inflammatory property of ginger in rheumatoid arthritis is getting attention nowadays because of its functional components like gingerols and shogaol that can dominate pain caused by rheumatoid arthritis. These compounds can potentially inhibit the proliferation of prostaglandin, leukotriene, and the activation of cytotoxic T-cells. This review aims to update the data on the anti-inflammatory effect of ginger with its potential phytoconstituents.

Keywords: Rheumatoid arthritis, Disease activity, Herbal, Ginger, Anti-inflammatory, Phytoconstituents

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Introduction

With over 100 distinct varieties, arthritis is a common health problem for millions of adults. Rheumatoid arthritis (RA) and osteoarthritis (OA) are the two most prevalent kinds. A biomechanical and inflammatory condition, arthritis is impacted by age, obesity, metabolic

diseases, injury, and mechanical and oxidative stress. Alterations in the bone, synovitis, and degradation of the joint cartilage typify it (Lindler *et al.*, 2020). Multiple joints are affected by the systemic disease known as rheumatoid arthritis, characterized by immunological dysregulation and inflammation. Genetics, smoking, and feminine gender are risk factors. Seropositive individuals see more inflammation and joint injury compared to sero-negative people (Chukwudi *et al.*, 2020). Treatment for RA is difficult; current options include NSAIDs, pain relieving agents, SNRIs, and intra-articular mediated corticosteroids. Research indicates that 1.3% of RA patients on NSAID therapy had major GIT concerns annually. Additionally, these may result in hepatic dysfunction and renal complications, which include irreversible and reversible papillary necrosis. Traditional immune -modulating antirheumatic drug (DMARD) monotherapy, especially methotrexate and cyclosporine, is essentially suggested for early-phase RA patients and established RA patients; however, side effects may limit their use, and concerns about the drug toxicity, drug safety, and expense of traditional therapies limit their uses and give focus on natural therapies and herbal therapies to serve safe and effective treatment. Particularly plants have proven to be a useful source of bioactive substances with therapeutic uses (Khamkat *et al.*, 2022a). One such plant is ginger (*Zingiber officinale*), Zingiberaceae (family) is renowned for its calming and tranquilizing effects and potential health benefits due to its anti-inflammatory properties at nerve joints (Chandra *et al.*, 2019). This review study aims to look into the analgesic effects of ginger extract on inflammatory responses. Arthritis is characterized by joint swelling and discomfort, which exacerbates with age and produces pain, incapacity, stiffness, and restricted range of motion. Conventional anti-inflammatory drugs frequently have drawbacks, such as indigestion and stomach ulcers. Consequently, looking into natural (Thakor *et al.*, 2023) substitutes like ginger extract can offer a sustainably safer solution to joint inflammation. Bioactive substances, such as polyphenols, flavonoids, terpenoids, phenolic ketones, oleoresin, aldehydic hydrocarbons, and essential oils, are known to be present in ginger and to have a variety of therapeutic uses (Khamkat *et al.*, 2022b). These substances have strong anti-inflammatory properties against various macrophages and eicosanoids, such as prostaglandin (PGE) and leukotriene (Wicaksana *et al.*, 2011). This effort tries to pinpoint the precise molecules causing the observed anti-inflammatory action by extracting and analyzing the active ingredients from ginger. The market is filled with pharmaceutical solutions, but there has been a steady increase in demand for natural and plant-based therapies. The World Health Organization (WHO) defines rheumatoid arthritis as an auto-immune disorder and in this illness, an individual's immune system fails to identify its tissue. These include people with compromised immune systems, such as those who are obese, overweight, or have weak muscles due to joint wear and strain (Juwita *et al.*, 2018). Anti-inflammatory drugs are often used to treat inflammation. Depending on the severity and site of the origin of inflammation, these drugs may be used locally or systemically. The advent of synthetic commercial anti-inflammatory drugs has resulted in adverse effects and serious contraindications with certain drugs (Kim *et al.*, 2022). These consist of inhibition of platelet function, suggesting that anticoagulant use should be avoided, diminishing the effects of diuretics and beta blockers' antihypertensive action, rapid excretion of the drugs due to hydroxylation in the liver, and boosted nephrotoxicity from cyclosporine. Research on natural substances having anti-inflammatory properties may help to create novel therapeutic options and support international efforts to combat autoimmune rheumatoid arthritis. Scientists and academics have been investigating possibilities for using plant extracts to create potent anti-inflammatory tinctures, tablets, and capsules for arthritis in recent years. As per the WHO, a medicinal plant

includes active chemicals that may possess therapeutic value or precursors for beneficial pharmaceuticals. Numerous investigations on the anti-inflammatory properties of ginger extract and its components have shown encouraging findings (Shao *et al.*, 2010). Furthermore, ginger extract has the benefit of being widely available and plentiful. Because of its accessibility, anti-inflammatory ointments may be produced sustainably, especially in areas where pain is common and access to traditional therapies may be restricted. With its wide range of bioactive components, ginger extract with shagaol and gingerol has an encouraging potential as a painkiller (Mutthuraj *et al.*, 2020). To sustain the drug release profile, ginger ointments can be a better alternative as having no side effects. By tapping into the power of nature, Ginger extract may provide a natural and effective solution for individuals suffering from gouty inflammation in arthritis, contributing to the advancement of holistic healthcare practices (Ma *et al.*, 2021).

Pathophysiology of Rheumatoid Arthritis (RA)

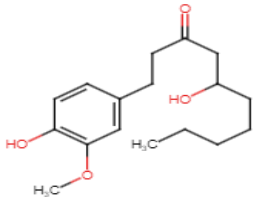
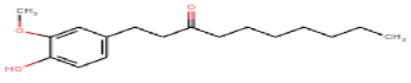
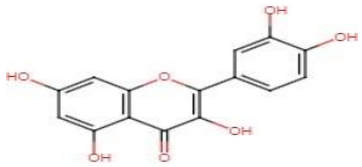
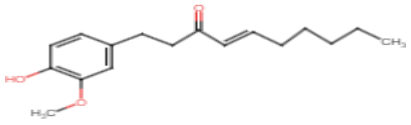
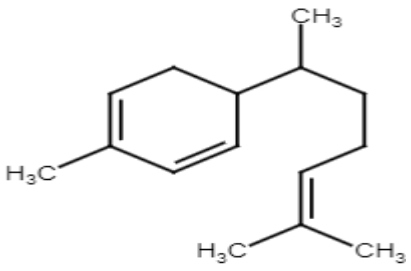
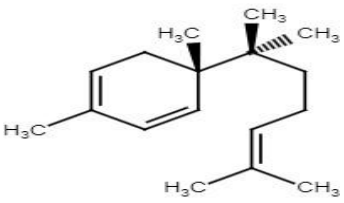
The pathophysiology and the progression of rheumatoid arthritis consist of a convoluted series of actions culminating in tissue damage (Funk *et al.*, 2016). N4β1-integrin is expressed by active T lymphocyte cells, and it binds to cellular molecules by vascular adhesion to enable them to pass through extracellular fluid (Ali *et al.*, 2022). T lymphocytes are activated by antigens like class II major histocompatibility complex (MHC). T cells are differentiated into T helper 1 (TH1) and T helper 17 (TH17) via interleukins (IL) like IL-17, IL-1, IL-6 and IL-23, T cell receptor (TCR), tumor necrosis factor (TNF), and transforming growth factor (TGF). The production of cytokines, such as IL-18 and receptor activator of nuclear factor κB (RANKL), causes synovial fibroblasts and chondrocytes to generate enzymes that break down bone (Kumar *et al.*, 2013), speeding up the course of RA. After fibroblast activation, inflammation develops, and cytokines such as TNF, IL-1, and IL-6 strictly lead to chronic inflammation (Ozkur *et al.*, 2022).

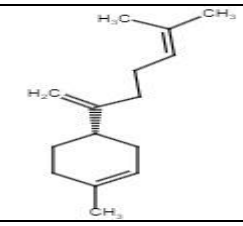
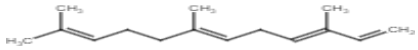
Zingiber officinale's beneficial impact on Arthritis

For generations, people have utilized the medicinal herb ginger to relieve joint discomfort caused by rheumatoid arthritis (Sawanny *et al.*, 2023). Several scientific studies show evidence of having anti-inflammatory properties of ginger because it prevents the production of prostaglandins and leukotrienes. Research has indicated that ginger may help lessen RA-related inflammation (Jafarzadeh and Nemati, 2018). It has been reported that high dosages of ginger in rats dramatically lowered PGE2, suggesting that ginger may have anti-inflammatory properties. Ginger contains various phytochemicals. Phenolic substances such as shogaols, paradols, and gingerols; sesquiterpenes like sesquiphellandrene, curcurmene, bisapolene, zingiberene, and zingiberol; vitamins such as thiamine, riboflavin, niacin, pyridoxine, A, C, and E; ginger glycolipids; monoacyldigalactosyl glycerols; zingerone; geraniol; gingesulfonic acid; galanolactone; 6-Dehydrogingerdione and geraniol are present in ginger (Table 1) having different pharmacological properties (Main and Whittle, 1975). By preventing the formation of PGE2, gingerol has pain-relieving and anti-inflammatory properties. Additionally, research has shown that ginger helps lessen arthritis-related pain and inflammation. In individuals suffering from rheumatoid arthritis, and muscle soreness, ginger oil has also anti-inflammatory and anti-arthritic properties. Ginger also can suppress COX-2 enzymes, which helps lessen inflammation. It is also shown that inactivating macrophages might lessen inflammation (Yadav *et al.*, 2022). Additionally, it has been discovered that ginger extract prevents LPS-induced macrophages from releasing proinflammatory cytokines and chemokines. All the studies have indicated that ginger may be useful as a natural anti-inflammatory to lessen arthritis-related pain and inflammation (Kravchenko *et al.*, 2019).

The RAW 264.7 cell line assesses the pharmacological effects of 14 phytochemicals produced from *Zingiber officinale* through a series

Table 1: Structure of some phytoconstituents present in ginger extract

Phytoconstituents	Structure
Gingerol	
Paradol	
Quercetin	
Shagaol	
Zingeberene	
Beta Sesquiphellandrene	

Beta Bisabolene	
Alpha Fernesene	

of tests. Scientific literature provides knowledge and information about how 10-gingerdione, 1-dehydro-10-gingerdione, and 6-shogaol dramatically lowered intrinsicnitric oxide synthase (iNOS) expression while greatly reducing LPS-induced nitric oxide generation. Experiments both *in vivo* and *in vitro* are used to evaluate the anti-inflammatory properties of 6-gingerol. 6-gingerol has been shown to have anti-inflammatory properties as evidenced by its considerable reduction in lysosomal enzyme levels and inhibition of lactate dehydrogenase and acid phosphate. Toll-like receptors (TLRS) are essential for inflammation in rheumatoid arthritis. Because of inhibiting NF-κB activity, *Zingiber officinale* may be a viable therapeutic target for autoimmune and inflammatory illness (Srivastava and Mustafa, 1992).

Ginger can be used as an active pharmaceutical ingredient (API) in the preparation of ginger ointment. The ointment bases are such as anhydrous lanolin (wool fat), hydrous wool fat (mixture of 70% w/w wool fat and 30% w/w purified water), wool alcohol, beeswax, carbowax, white petrolatum, mineral oil which serves as a carrier for the API (Leach and Kumar, 2008). Preservatives prevent microbial growth such as methyl paraben, propyl paraben, benzyl alcohol, sodium benzoate, potassium sorbate, and benzalkonium chloride. Antioxidants protect the formulation from oxidative degradation such as ascorbic acid, BHA, BHT, and tocopherol. Emulsifier promote the stability of ointment such as glyceryl monostearate, lecithin, coconut oil (natural emulsifier), glyceryl monooleate, triethanolamine stearate alcohol, cetyl alcohol, divalent calcium ions. Permeation enhancer is used to increase the permeation through the skin such as terpenes, oleic acid, amides, and olive oil. These excipients are used for preparing ginger ointment.

Preparation procedure:

Soxhlation extraction of ginger roots

The roots of the ginger plant are cleaned, dried, and ground into powder. To create pure extracts, it is combined with methanol in a Soxhlet apparatus, and filtered. The solvent is evaporated to concentrate the filtrate (Khamkat *et al*., 2024).

Preparation of ointment contains ginger extracts

An ointment can be prepared by the emulsification method. In this method, at first, the base and oil components are melted in a serological water bath at 65^{0}C. The water-soluble components are melted at the same temperature as the base separately. Then the solution is slowly added to the melted base with continuous stirring until solid particles are properly dissolved. As per the standard procedure, the API is then added after the mixture is cooled down to 50^{o}C. Next, put the mixture in a mechanical stirrer to make a uniform ointment (Aiyalu *et al*., 2016).

Evaluation Parameters of Ginger Ointment

Pre-formulation study of ginger: To create a stable dosage form, the study includes a pre-formulation study. Solvents such as ethanol, acetone,

chloroform, and distilled water are used in solubility analysis. An estimate of the extract's melting point is made by the melting point apparatus (Shao *et al*., 2010). Using phosphate buffer 6.8, the UV-VIS Spectrophotometric technique is used to confirm the drug.

Organoleptic studies: This study examines the impact of storage on ointment compositions through organoleptic testing, focusing on physical characteristics like color, dose form, odor, and consistency.

Homogeneity: The homogeneity test ensures a uniform blend of active ingredients, basic ingredients, and essential additives in ointment manufacturing. It measures the texture of glass objects, and no variations are found after 15 days of storage. The non-irritative and homogeneous nature of the ointments is confirmed.

Adhesion: The adhesion test investigated the ointment's skin-applied retention period. Excellent adherence indicates a long-lasting ointment. Timing the amount of time, it took for the ointment to release onto the plate served as the test. The timing to detach from the ointment slab was 6.5 sec, confirming their good adhesion power.

pH: The pH level should be maintained because the imbalance of pH level can cause an irritating sensation on the skin. The skin pH range lies between 5.6-5.9. More acidic pH can cause irritation in skin and more basic pH can cause scaly skin.

Viscosity: A Brookfield digital viscometer is used to test the viscosity of topical formulations, with shear rates ranging from 1-4 r.p.m. for one minute at 25°C (Minghetti *et al*., 2007).

Skin irritation: Ointment is applied to the skin. Then adhesive strips are adhered in that area. Then erythema is detected and assessed to confirm the safety of ointment.

Water washability: The required amount of test ointment is rubbed on the hand for 2-3 min and washed with water to assess washability.

Spreadability: The term "spreadability" describes how well an ointment adheres to skin or other affected regions. It is essential to an ointment formulation's bioavailability efficiency. Spreadability is defined as the ability of an ointment to spread on the skin after application under a specific stress. The higher the spreadability indicates the shorter the separation time. The herbal ointment is applied to one glass slide and sandwiched between the other in two sets of glass slides. After that, the slides were secured to a platform and the weight are taken off. Spreadability is calculated using the formula:

$$S = M. L / T$$

Where, M= weight, tied to the upper slide, L = length moved on the glass slide, T = Time taken for the separation of the slides (Desai and Mhaskar, 2019).

Drug Content Determination: Plotting the slope and intercept at maximum wavelength allows for the spectrophotometric estimation of 0.1 g of the formulation after it has been dissolved in phosphate buffer 6.8 and filtered.

Compatibility studies by FT-IR: Drug-polymer compatibility is confirmed by FTIR Spectroscopy, which compared ginger extract with other excipients. For interpretation, wave numbers are compared to pure samples.

In-vitro Release/Permeation Studies: Franz diffusion cells and egg membranes are used in *in vitro* release experiments. After equally spreading pre-weighed ointment, samples are taken and their drug concentration is measured with a UV-visible spectrophotometer at maximum wave length (Shao *et al*., 2010).

Stability Studies: To the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) requirements, stability experiments are carried out on the optimized formulation (Lee *et al*., 2022). Samples are kept at different temperatures and monthly analyses are done to check for drug concentration, pH, clarity, and visual appearance.

They are assessed for physical characteristics and product integrity after three months.

Future aspects

The utilization of natural compounds for their therapeutic properties has gained significant attention in recent years. Plants, in particular, have been a valuable source of bioactive compounds with diverse medicinal properties. One such plant is Ginger (*Zingiber officinale*), which is not only renowned for its demulcent and carminative effect but also possesses an anti-inflammatory sensation at nerve joints as a potential health benefit. This article aims to investigate the analgesic activity of ginger extract against inflammatory response (Mutthuraj *et al*., 2020). Arthritis, swelling, and tenderness of joints cause pain, disability, stiffness, and reduced range of motion that worsen with age. By extracting and characterizing the active components from Ginger, this project aims to identify the specific compounds responsible for the observed anti-inflammatory activity. In conclusion, the exploration of plant-derived compounds for their pain-relieving properties has new avenues in the development of alternative treatments. Ginger extract, with its diverse array of bioactive compounds, shows promising potential as a pain-relieving agen t(Funk *et al*., 2016). Further research and development are necessary to harness its full therapeutic benefits and determine the optimal formulation for anti-inflammatory ginger ointments. By tapping into the power of nature, Ginger extract may provide a natural and effective solution for individuals suffering from gouty inflammation in arthritis, contributing to the advancement of holistic healthcare practices.

Recent Developments

The discovery and creation of novel ginger formulations, such as tablets, capsules, powder, cream, gel, transdermal patches, nanoparticles, neosomes, liposomes, and phytosomes, as well as their therapeutic action by enhancing bio-availability, therapeutic effect, and delivery in recent years, are future research areas (Londhe *et al*., 2021). Recently, ginger extract solid dispersion (GE-SD) packaged in a starch/chitosan composite film has been developed as a gastro-retentive expandable film to allow the controlled release of ginger extract for the treatment of gastric inflammatory disease (Kaewkroek *et al*., 2022). Ginger and castor oil are used to develop a nanostructured lipid carrier (NLC) as an innovative delivery system for the treatment of rheumatoid arthritis. Achievements in the study of streptococcal cell-induced arthritis using cedrol, a sesquiterpene with anti-inflammatory qualities found in ginger (Zhang *et al*., 2021).

Conclusion

The phytochemical components of ginger in the form of ointment may be able to treat both the disease and its symptoms of RA. Novel medications for the treatment of RA damage and symptom alleviation may result from a deeper comprehension of these pathways. It has been discovered that main ginger component that is gingerol and shagaol have strong anti-inflammatory properties, with gingerols preventing LPS-induced COX-2 production. In research, of 261 individuals with arthritis, the analgesic impact of ginger extract was assessed; 94.6% of patients reported a decrease in pain. A thorough investigation into the mechanism of COX-2 inhibition by ginger extract revealed that 8-paradol and 8-shogaol markedly decrease COX-2 enzyme activity. Because of having anti-inflammatory activity, ginger can be used as a complementary to synthetic non-steroidal anti-inflammatory drugs (NSAIDs) and in the form of ointment can give a sustained release profile of the drug.

Conflict of Interest

The authors declare no conflicts of interest.

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