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Review Article

Modern Phyto-Emulgel Platforms of Lemongrass oil for Rheumatoid Arthritis

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ABSTRACT

The systemic autoimmune disease known as rheumatoid arthritis (RA) is typified by progressive cartilage degradation, synovial hyperplasia, and persistent joint inflammation. Long-term use of systemic medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), is frequently linked to serious gastrointestinal, hepatic, and renal adverse effects, even though there are seversal pharmacological therapies available. As a result, there is growing interest in localised, plant-based treatments that are effective while having little systemic toxicity. Rich in bioactive substances including citral and geraniol, lemongrass (Cymbopogon citratus) essential oil has strong anti-inflammatory, analgesic, and antioxidant qualities, making it a viable option for the treatment of RA. Aim- The purpose of this study was to develop and assess a topical emulgel loaded with lemongrass oil in order to improve medication absorption via the skin and offer focused, long-lasting alleviation of RA symptoms. The methodology: An oil-in-water emulsion was mixed with lemongrass essential oil to create an emulgel formulation, which was then stabilised using non-ionic surfactants and gelled with Carbopol 940. The formulation's physicochemical characteristics, such as its drug concentration, pH, viscosity, and spreadability, were described. Franz diffusion cells were used in ex vivo skin penetration and in vitro release investigations. Using the Freund's Complete Adjuvant (FCA)-induced arthritis paradigm in Wistar rats, anti-inflammatory effectiveness was assessed in vivo by measuring joint thickness, paw oedema, and synovial tissue histology. Results: The optimised emulgel showed constant medication content, good physical stability, and skin pH compatibility. Studies on drug release in vitro showed a 12-hour sustained release profile. When compared to simple formulations, ex vivo permeation experiments verified improved skin absorption of lemongrass oil. Paw oedema, joint inflammation, and pro-inflammatory cytokine production (TNF-α, IL-6) were all significantly reduced in the treated groups, according to in vivo data. Histological analysis confirmed the anti-inflammatory impact by

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showing less infiltration of inflammatory cells and thickening of the synovial membrane. In conclusion- the emulgel filled with lemongrass oil showed great promise as a natural, non-invasive topical treatment for rheumatoid arthritis. It is a viable supplement or substitute for traditional RA therapies since it can directly reduce inflammation in afflicted joints without causing systemic negative effects. In order to confirm its effectiveness in human patients, more clinical research is necessary.

INTRODUCTION

RA is a chronic, systemic autoimmune disease primarily affecting synovial joints. Characterized by persistent synovitis, systemic inflammation, and autoantibody production, RA leads to progressive joint destruction, functional disability, and reduced quality of life. It affects approximately 0.5–1% of the global population, with a higher prevalence in women than men. The disease involves complex interactions between genetic, environmental, and immunological factors. RA is considered a multifactorial disease, with risk factors including smoking, infections, hormonal influences, and certain genetic markers like HLA-DR4. The autoimmune response in RA is characterized by the activation of T-cells, B-cells, and macrophages, which collectively contribute to the production of inflammatory cytokines such as TNF-α, IL-1, and IL-6. These cytokines play a key role in perpetuating synovial inflammation and joint destruction. Moreover, systemic inflammation in RA is not limited to the joints but can also involve other organs, leading to complications such as cardiovascular disease, interstitial lung disease, and osteoporosis.(1) Both non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis caused by crystal deposition (pseudogout, basic calcium phosphate disease, gout), bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhoea, complications of Lyme disease, Parvovirus, Enterovirus), or autoimmune processes are among the many types of arthritis that have been studied and described.(2) Systemic lupus erythematosus (SLE), Sjögren's syndrome, adult-onset scleroderma, spondylarthritis (SpA), psoriatic arthritis (PsA), polymyositis (PM), and other conditions are also included in the diverse category of autoimmune rheumatic illnesses. Even though their indications and symptoms could be identical, a differential diagnosis is crucial.(3)The aetiology of RA remains unclear despite the proposal of several biomolecular processes. One theory currently in use is that anti-citrullinated protein antibodies (ACPAs) are produced because of dysregulated citrullination.(4) With sporadic flare-ups, RA progresses in a variable manner. Without the best care, symptoms progressively increase until the joints are irreparably damaged and compromise both physical and mental functioning. Additionally, comorbidities and problems associated with RA shorten patients' life expectancy by a few years. (5) Below **image no.1** shows pathology and epidemiology of RA.

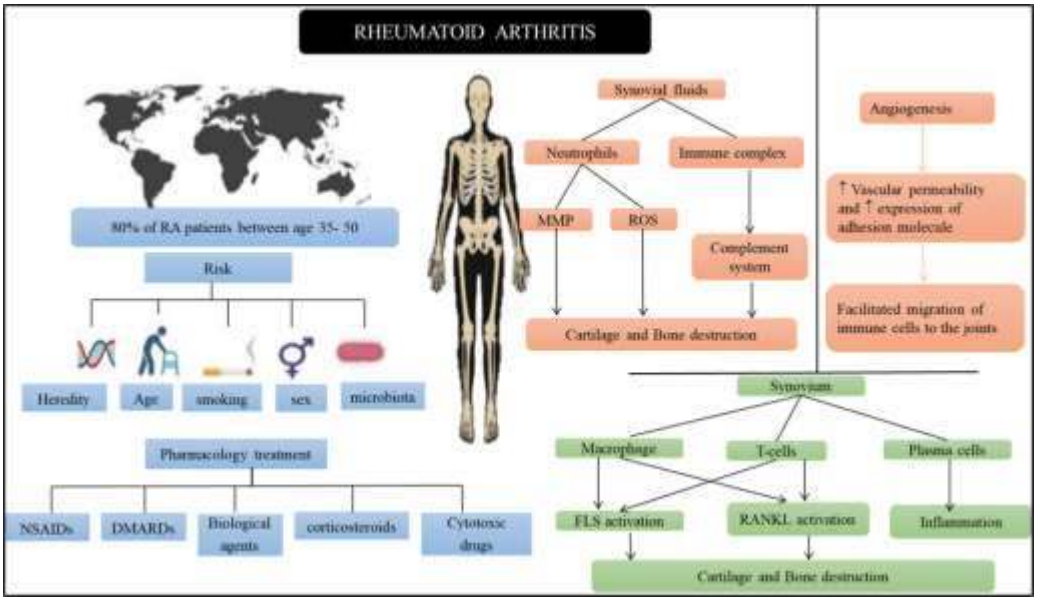


Figure 1: Pathology, Risk factor & treatment of Rheumatoid Arthritis.

DMARDs, corticosteroids, biologics, and NSAIDs are all part of the traditional pharmacological care of RA.(6) Although these treatments can reduce inflammation and moderate the course of the disease, long-term use of them is frequently linked to negative side effects, such as hepatotoxicity, cardiovascular risks, immunosuppression, gastrointestinal bleeding, and an increased risk of infection. Furthermore, the investigation of safer and more economical alternatives is required because to the high expenses and partial or non-response in a fraction of patients.(7)

A potential method for treating RA, especially localised joint inflammation, is topical medication administration. Topical solutions can decrease systemic adverse effects, avoid first-pass metabolism, and increase patient compliance while delivering focused activity.(8) In this regard, natural products have drawn interest; one such option is the essential oil of Cymbopogon citratus, also known as lemongrass. Lemongrass oil is a promising treatment for inflammatory diseases like RA because of its strong anti-inflammatory, analgesic, and antioxidant properties, which are attributed to its high citral content (a blend of geranial and neral).(9,10)

However, essential oils have drawbacks that limit their absorption and therapeutic effectiveness in traditional formulations, including volatility, instability, and low water solubility. The advantages of both dosage forms are combined in emulgels, which are hybrid systems of emulsions and gels that provide a flexible drug delivery platform. They solve the problems with volatile oils by offering better medication solubilisation, skin penetration, and prolonged release. Additionally, nano-emulgel systems can improve medication penetration and retention at the target location because of their higher surface area and smaller droplet size.(11)

The purpose of this study is to create and assess a topical nano-emulgel loaded with lemongrass oil for the treatment of RA. Using a rat paw oedema model caused by carrageenan, the study includes formulation optimisation, physicochemical characterisation, in vitro drug release analysis, and in vivo anti-inflammatory testing. This study aims to provide a safer, more efficient, and more patient-friendly option for treating RA by using the therapeutic potential of lemongrass oil and the sophisticated delivery advantages of nano-emulgels.

2. LITERATURE REVIEW

2.1. RA Pathology-The immunological mechanisms that occur in the joint synovium and synovial fluid are of interest, even if the precise aetiology of RA is still unclear. TNF-α, IL-1, and IL-6 are among the cytokines released by synovial macrophages as part of these immunological responses.(12–14) These cytokines speed up bone degradation by co-stimulating osteoclast activity with inflammation and FLS. Moreover, active FLS can create matrix metalloproteinase (MMP), which degrades cartilage. Nuclear factor-kappa-light-chain-enhancer of activated B cells (NF-κB) is involved in the pathogenesis of chronic inflammatory diseases. FLS triggers the NF-κB signalling pathway, which allows T cells to adhere to proteins on the surface of osteoclasts.(15) This accelerates the deterioration of bone by increasing osteoclast activity. FLS can cause symmetrical joint degeneration by spreading from one joint to another, as is typical in RA. Additionally, autoantibodies, the most prevalent of which are RF and ACPA, are found in the blood of RA patients.(16) These autoantibodies are present in 50–80% of RA patients, along with newly identified antibodies such as anti-acetylated protein and anti-carbamylated protein antibodies. The production of antibodies causes inflammation, and citrullination triggers an immune reaction that initiates the manufacture of ACPA. (17)The existence of ACPA in RA patients is directly associated with bone loss and pain, and it might play a major role in the chronic inflammatory process. The heart, kidneys, lungs, digestive system, eyes, skin, and neurological system are frequently impacted in addition to joints since RA is a systemic disease. About 40% of those with RA experience issues.(18) This image no-2 shows the sign and symptoms of RA.

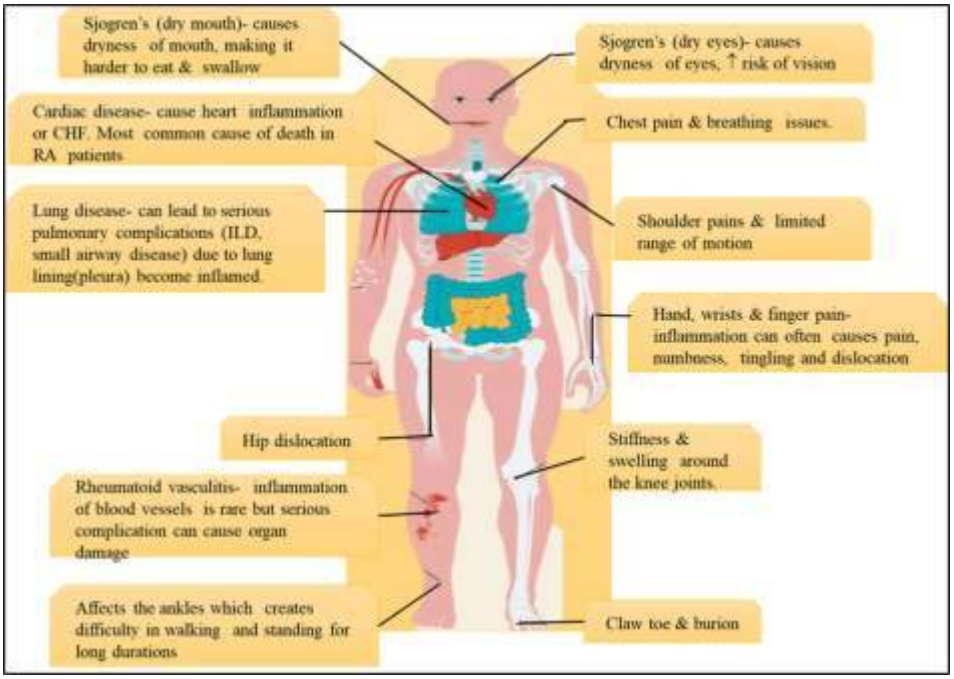


Figure 2: The List of various clinical complications of Rheumatoid Arthritis

2.2. RA Treatment Limitations- Currents treatments of RA contains different type of managements as shown in image no-3. Trial-and-error treatment is frequently used for patients with difficult-to-treat RA, which can be troublesome for a number of reasons. Up to 20% of RA patients still have a difficult-to-manage condition, despite the fact that RA medication has made substantial

progress in recent decades. The current therapies for RA include DMARDs, corticosteroids, NSAIDs, and biological DMARDs. Additionally, these drugs stop joint deterioration. (19)

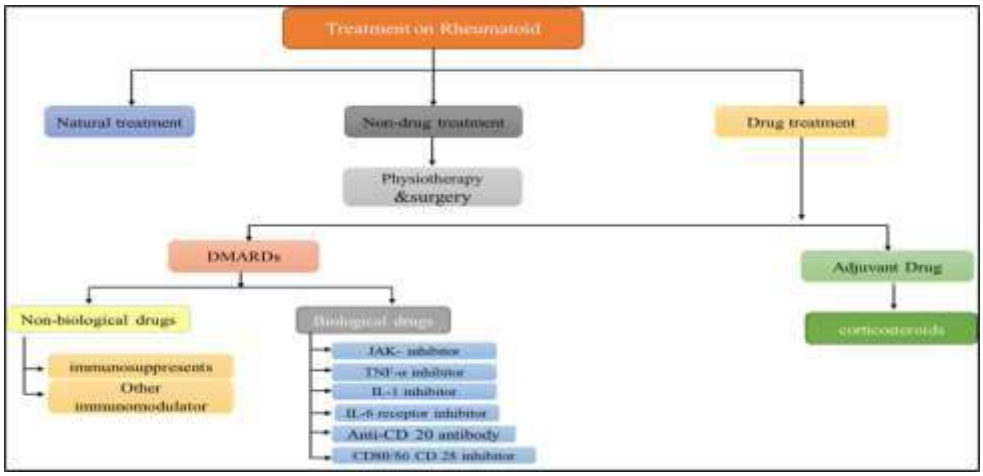


Figure 3: An overview of current treatment of Rheumatoid Arthritis.

Concerning the use of glucocorticoids, biologic DMARDs, and DMARDs in high-risk populations, including those suffering from cancer, congestive heart failure, hepatitis, and other serious illnesses. Patient demand, cost, and tolerance are the key determinants for designing such combo therapy. Biologic DMARDs can exacerbate the illness and can result in flare-ups if stopped abruptly. In all cases, a patient's comorbidities, financial choices, tolerance, and the severity of their condition should be considered before a doctor and patient mutually choose a course of treatment. Conventional treatments for RA, including methotrexate (MTX), sulfasalazine, leflunomide, and others, can have serious side effects, including teratogenicity, gastrointestinal distress, bone marrow suppression, and hepatotoxicity. Biologic medications increase the risk of infections, malignancies, and cardiovascular problems. Regular checks of blood levels, liver function, and infection symptoms are necessary for patients. (20) Table no. 1 shows the drugs which are used in RA and adverse effects.

Careful supervision is necessary to balance the therapeutic benefits with any potential drawbacks in order to guarantee patient safety and therapy efficacy.

Table No-1: Drugs with their reported adverse effects.

Sr.No	Drug class	Drug name	Adverse effects	Reference
1.	NSAIDs	Naproxen Aspirin Flurbiprofen Ibuprofen	inflammation of the stomach, peptic ulcer, bleeding in the stomach, Feeling queasy, pain in the abdomen, kidney dysfunction, impacts on the heart, Rash	(21)
2.	Corticosteroids	Prednisone, Hydrocortisone Methylprednisolone Dexamethasone	Diabetes, osteoporosis, metabolic syndrome, cataracts, and peptic ulcers.	(22,23)
3.	Conventional synthetic DMARDS	Methotrexate	gastrointestinal problems, hepatic dysregulations, pneumonitis, and renal damage.	(24)

		Hydroxychloroquine	Gastrointestinal conditions Disorders of the skin Toxicology of the retina	(25,26)
		Sulfasalazine	Leukopenia, agranulocytosis, central neurological toxicity, fertility issues, and kidney failure	(27)
		Leflunomide	Migraines, vomiting, abdominal cramps, elevated blood pressure, and an organ failure the liver	(28)
4.	Biological DMARDs (TNF-α Inhibitors)	Etanercept Infliximab. Adalimumab Certolizumab Golimumab Certolizumab pegol	Upper airway infections, vomiting, breathing difficulties, and arterial hypertension	(29)
5.	Targeted synthetic DMARDs (Janus Kinase inhibitor)	Tofacitinib	infections, elevated serum transaminases, a high cholesterol level, and creatininemia.	(30,31)
		Baricitinib Upadacitinib	Infections Neutrophils reduce migraines and dermatitis.	
6.	Biological DMARDs (IL-6 Receptor inhibitor)	Tocilizumab	infestations as well as infections, Skin rashes and elevated blood pressure.	(32)
		Sarilumab	infestations as well as infections, Neutropenia Elevated LDL cholesterol (low-density lipoprotein)	(33)

3. LEMONGRASS : TRADITIONAL USES AND PHYTOCHEMISTRY

The Poaceae grass family includes the tall perennial plant known as lemongrass (Cymbopogon), which grows well in tropical and subtropical climates. Steam distillation is the method used to extract lemongrass oil from the plant's dried leaves. It is either brilliant yellow or pale, and it has a thin consistency. It smells powerful, fresh, earthy, and citrussy. In addition to relieving rheumatism and muscular soreness, lemongrass oil may assist tone and relax your muscles. Geranyl acetate, myrcene, nerol, citronellal, terpineol, methyl heptenone, dipentene, geraniol, neral, farnesol, limonene, and citral are the primary constituents of lemongrass oil.

According to studies, limonene, another advantageous component of lemongrass, helps destroy germs and lessen inflammation. One of the top six essential oils with anti-inflammatory qualities is lemongrass oil.(34)

In India, lemongrass is a plant that is utilised for both medical purposes and scents. Lemongrass's extensive phytochemical composition is primarily responsible for its medicinal usefulness. Citral, a blend of two isomers—geranial and neral—is the most potent of the concentrated bioactive chemicals found in the essential oil that is produced from its leaves and stalks. The plant's potent lemon aroma and several pharmacological characteristics, such as its anti-inflammatory, analgesic, antifungal, antibacterial, and antioxidant actions, are mostly caused by these constituents. Limonene, myrcene, geraniol, and linalool are other significant components of

lemongrass oil that work in concert to enhance the plant's overall bioactivity.

The anti-inflammatory properties of lemongrass are especially significant from a pharmaceutical standpoint. In a variety of in vitro and in vivo settings, citral has been demonstrated to suppress the synthesis of pro-inflammatory mediators such prostaglandins, nitric oxide (NO), and cytokines like interleukin-1β (IL-1β) and TNF-α. In the context of chronic inflammatory diseases like RA, where immunological dysregulation and persistent inflammation are key factors in the development of the illness, these processes are particularly intriguing.

Furthermore, by shielding tissues from oxidative stress, a recognised cause of RA-related joint damage, lemongrass's antioxidant qualities—which stem from its capacity to scavenge free radicals and suppress lipid peroxidation—may offer further therapeutic advantages. The plant's potential as a supplemental or alternative medicinal agent is highlighted by these two actions: lowering oxidative damage and controlling inflammation.(35)

3.1. Anti-inflammatory Activity of Lemongrass Oil

The use of traditional drugs to treat painful conditions including sciatica, cluster headaches, arthritis, and others was restricted because of their severe adverse effects.(36) Scientists continue to look for new natural medications that are very effective and have fewer adverse effects in spite of this findings. Among the many therapeutic plants with strong anti-inflammatory qualities is C. citratus. As a result, C. citratus was extensively studied in vivo utilising animal models. Researchers used the carrageenan-induced rat pas oedema model to investigate the anti-inflammatory properties of several C. citratus fractions, such as the flavonoid and tannin fractions. The authors observed that while both fractions were rich in bioactive chemicals, particularly luteolin, the combination of them decreased the oedema volume by about 59%.(37)

It has been demonstrated that this bioactive derivative inhibits the production of proinflammatory factors such cytokines, iNOS, TNF-α, IL-ß, and IL-6. In the same setting, researchers demonstrated that the fractions high in phenolic acid and tannin suppress the activation of NF-θb in both human and murine macrophages that have been pretreated with various C. citratus fractions. Furthermore, these authors suggested that fractions of C. citratus had a significant reduction in the production of nitric oxide and a significant decrease in the proteasome activity of murine macrophages activated by LPS, which may account for the anti-inflammatory properties of C. citratus, which is thought to be a promising source of safe and active substances.(38,39)

LEO's strong anti-inflammatory qualities, which have long been used in traditional medicine to reduce pain and swelling, have drawn increasing scientific interest. It has been demonstrated that the oil's main active ingredients, citral, geranial, and neral, inhibit the synthesis of pro-inflammatory cytokines and enzymes, which makes it useful for regulating immunological responses. The potential of lemongrass oil to lower inflammatory markers including VCAM-1, IP-10, and MIG in pre-inflamed human dermal fibroblasts has been demonstrated in recent investigations, offering a molecular explanation for its calming effects on inflammatory tissues.(40) Furthermore, it has been shown that geraniol, a significant component of lemongrass, activates protective cellular pathways such PI3K/Akt and Nrf-2, which results in the overexpression of heme oxygenase-1, an enzyme with anti-inflammatory and antioxidant

properties.(41) This implies that lemongrass oil helps shield tissues from oxidative stress in addition to reducing inflammation. Animal research also supports these conclusions; in zebrafish models, lemongrass essential oil showed notable decreases in oxidative damage and inflammation.(42) Furthermore, topical use of diluted lemongrass oil may provide comfort in illnesses such as rheumatoid arthritis, possibly complementing current medications with fewer side effects, according to some human experiences and early clinical findings. These encouraging findings imply that lemongrass oil may be a safe and efficient alternative for treating inflammatory diseases, particularly when applied topically using cutting-edge emulgel delivery technologies.(43) The below mentioned Figure-4 depicts that anti-inflammatory effects of lemongrass oil.

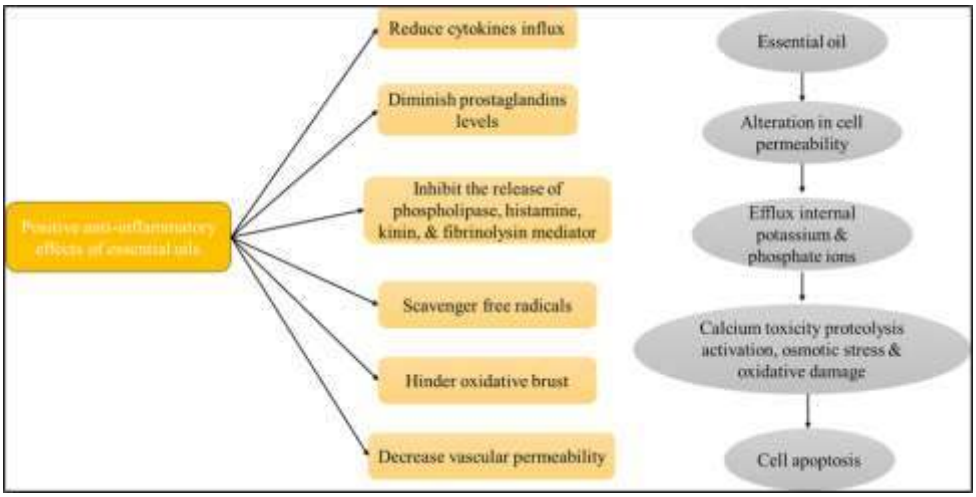


Figure 4: Anti-inflammatory effects of lemongrass oil.

4. THE ROLE OF TOPICAL DELIVERY IN RHEUMATOID ARTHRITIS (RA)

Any perfect formulation should have superior pharmacological activity, less side effects, self-administration, patient compliance, and non-invasiveness. The majority of the above described features are present in formulations administered topically. Avoiding the hepatic first-pass impact, reducing adverse effects because of the local site of action, improving percutaneous absorption, and maybe increasing bioavailability with a prolonged deposition are some advantages of topical administration.(44) Additional benefits include the capacity to precisely target the medicine at the intended spot and less drug loss from metabolism or breakdown. In the conventional treatment of RA, systemic therapy includes medications such as biologics, DMARDs, and NSAIDs. However, rising knowledge of the disadvantages of systemic medications, including unpleasant side effects, inadequate drug targeting, and the need for long-term administration, has spurred research into alternate therapy techniques, such as topical drug delivery. Applying medicinal materials directly to the skin to treat certain conditions is known as topical delivery, and it is a non-invasive method of medicine administration. Topical drug delivery systems (TDDS) have emerged as a promising approach for the targeted management of joint inflammation and pain in RA due to their many advantages over traditional systemic medicines.(45) Reduced drug breakdown combined with continuous administration of the medication over an extended length of time causes the drug to flow prominently across the stratum corneum barrier, improving bioavailability.(46) Numerous studies have demonstrated that topical administration of medications increases their

bioavailability. For instance, when administered topically as opposed to orally, flurbiprofen nano-emulsion demonstrated a 4.4-fold increase in bioavailability. The nile red dye nano-emulsion, which demonstrated a ten-fold increase in dye penetration into the skin in comparison to an emulsion formulation. A three-and-a-half increase in lacidipine bioavailability when administered transdermally with microemulsions. According to the group, this improvement could be the result of avoiding the drug's first-pass action when applied topically. A barrier to drug penetration, the stratum corneum (non-viable epidermis layer) is 5–20 µm thick and consists of ten to fifteen layers of thick corneocytes, lipid matrix, corneodesmosomes, and a tight junction. The following are some suggested routes for the molecule to get through the stratum corneum:

(a.) The paracellular (intercellular) pathway is the movement of a small lipophilic molecule between the corneocytes through the lipid matrix.

(b.) The lipophilic molecule splits into hydrophilic and lipophilic domains and then travels into the corneocytes via the transcellular (intracellular) pathway.

(c.) Drug molecules use the transfollicular (shunt) pathway to pass via hair follicles and sweat glands.

After passing through this non-viable layer (the stratum corneum), it disperses throughout the dermal layer and eventually reaches the blood vessels.(47) In this instance, the molecule will be able to cross the barrier by integrating into the proper carrier. Numerous nanolipid formulations have surfaced that have better penetration and longer residence durations than conventional topical preparations. These lipids also improve skin adhesion, which reduces water loss and enhances skin hydration, are biocompatible, and can lead to lipid exchange between carriers and the outermost layer of the epidermis, which facilitates drug penetration.

The below mentioned Figure-5 depicts that there are some pathways for the molecule to cross the stratum corneum.

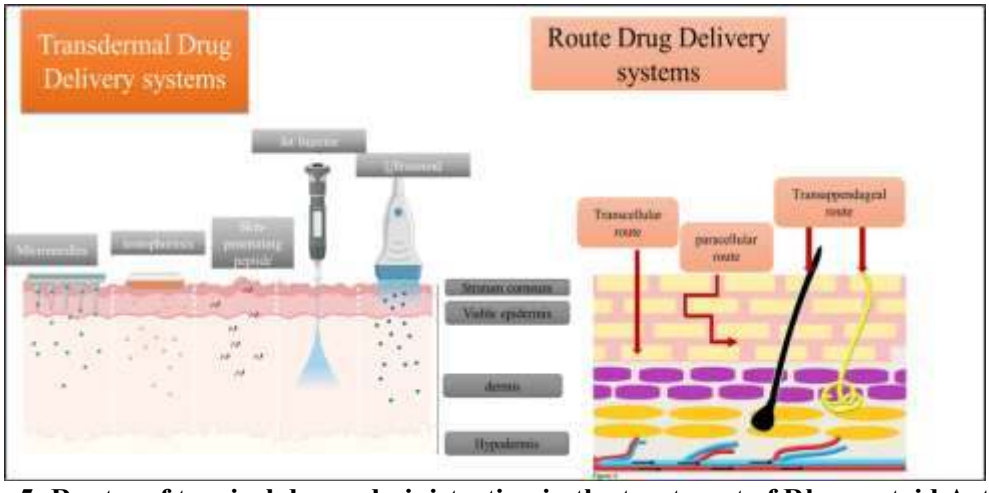


Figure-5: Routes of tropical drug administration in the treatment of Rheumatoid Arthritis.

Topical drug distribution is the process of applying a pharmaceutical formulation topically to the skin to produce localised action at the site of inflammation.(48) Even though the skin acts as a barrier, advances in formulation technology have made medications more effective and more soluble. Several topical formulations are used to treat RA, including gels, creams, ointments, patches. Among them, gels and creams are well-liked due to their ease of use and patient

compliance. These formulations often include NSAIDs including ketoprofen, ibuprofen, and diclofenac.(49) Studies have demonstrated that topical diclofenac gel significantly reduces pain and oedema in RA patients while having less gastrointestinal side effects than oral versions. Transdermal patches provide controlled, extended drug release. For instance, diclofenac and ketoprofen patches have shown promise in reducing inflammation and joint pain.(50) The primary disadvantage of conventional topical techniques is poor skin permeability, especially for hydrophilic or high molecular weight drugs.

Heterogeneous colloidal mixes of water and oil, with one component as a continuous phase and the other as a dispersed phase, are called nano-emulsions. At the interface between the continuous and dispersed phases, a surfactant called an emulsifier is adsorbed, reducing surface tension and stabilising the system. These systems have a longer shelf life than basic emulsions, micelles, suspensions, etc. because of their great thermodynamic stability.(51) Nano-emulsions are limited by their low viscosity, which results in low retention time and spreadability, despite their many benefits. These difficulties can be handled by converting the nano-emulsion into a nano-emulgel by employing an appropriate gelling agent.(52)

The nano-emulgel, which is a combination of gel and emulsion, functions as a colloidal system. Like other nano-carriers, the emulsion component enhances penetration and shields the medication from hydrolysis and enzymatic destruction. Maintaining the drug's therapeutic concentrations for an adequate amount of time is just as crucial as improving the drug's penetration through the skin. The gel component decreases surface and interfacial tension, increasing thermodynamic stability, and increases viscosity and spreadability, which enhance retention duration. Compared to other nano-carriers, nano-emulgel has a number of benefits, including a high drug loading capacity, improved penetration, diffusion, and little skin irritation.(53,54)

5. FORMULATION STRATEGIES FOR LEMONGRASS OIL-LOADED EMULGEL

In order to maximise the administration of both hydrophilic and hydrophobic medications via the skin, Emulgel, a complex topical drug delivery technology, combines the advantages of emulsions and gels. The volatile essential oil known as lemongrass oil (LGO), which comes from Cymbopogon citratus, is a great option for emulgel formulations because of its antibacterial, antifungal, antioxidant, anti-inflammatory, and analgesic qualities. The drawbacks of LGO, such as its limited water solubility, volatility, and potential for skin irritation due to its main component, citral, are addressed by the creation of lemongrass-loaded emulgel.

5.1. Lemongrass-Loaded Emulgel Ingredients-

Careful component selection is necessary for the formulation of lemongrass-loaded emulgel in order to guarantee stability, effectiveness, and skin compatibility. The oil phase, aqueous phase, emulsifiers, gelling agents, penetration enhancers, and the active ingredient, lemongrass oil, are the main components.

5.1.1. Oil Phase: Hydrophobic substances, such as lemongrass oil, are transported by the oil phase. Oils with occlusive qualities and improved skin penetration include oleic acid, liquid paraffin, and natural oils like argan oil. A study found that using lemongrass oil as an active component and penetration enhancer in an emulgel loaded with lornoxicam enhanced skin penetration and medication release.(55)

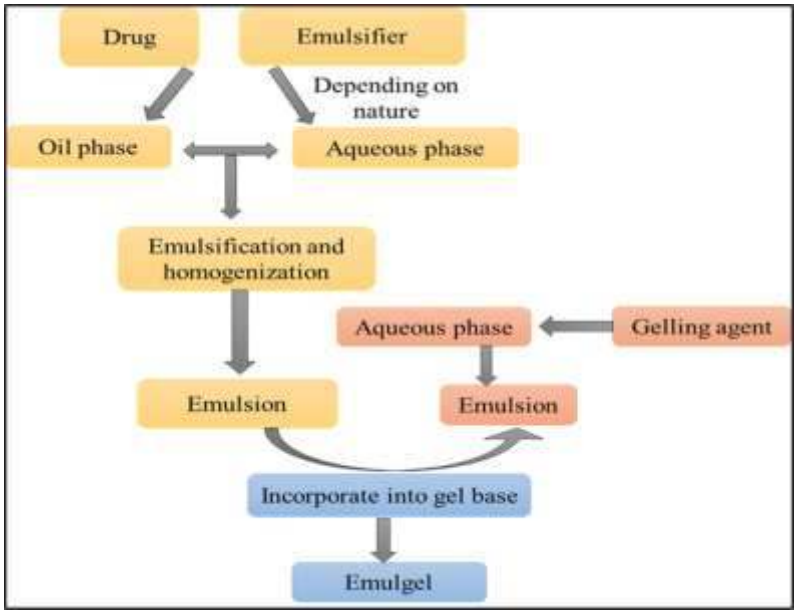
5.1.2. Aqueous Phase: This stage guarantees skin compatibility and is usually distilled water or a pH-adjusted buffer (pH 5.5–7.0). Propylene glycol and glycerin are examples of humectants that preserve moisture and enhance spreadability.

5.1.3. Emulsifiers: By lowering the interfacial tension between the aqueous and oil phases, emulsifiers stabilise the emulsion. Because of their low toxicity and skin compatibility, non-ionic surfactants like Tween 20, Tween 80, and Span 80 are preferred. A study created a meloxicam-loaded emulgel using Tween 20 and PEG 400, producing a stable microemulsion with globule sizes ranging from 128 to 176 nm.(56)

5.1.4. Gelling Agents: For prolonged drug release, gelling agents offer viscosity and thixotropic behaviour. Because Carbopol 934 and Carbopol 940 work well with emulsions, they are often utilised. According to a study, 1% Carbopol 934 produced an emulgel for glucosamine sulphate potassium chloride that had an 88% drug release over 6 hours (57). For biocompatibility, substitutes such as carboxymethyl cellulose (CMC) and hydroxypropyl methylcellulose (HPMC) are also utilised.

5.1.5. Penetration Enhancers: By rupturing the stratum corneum, lemongrass oil naturally improves skin penetration. According to a study on mefenamic acid emulgel, other enhancers like mentha or clove oil may be added.(58)

5.1.6. Active Ingredient: Lemongrass oil has broad-spectrum antibacterial and antioxidant properties due to its 60–80% citral, linalool, and citronellal content. Because of its weak solubility and volatility, it requires sophisticated delivery techniques, such as emulgel, to ensure stability and bioavailability.(59)



5.2. The Formulation Process-

Three crucial steps are involved in the methodical formulation of lemongrass-loaded emulgel in order to produce a stable, uniform product with the best possible drug release:

5.2.1. Emulsion Preparation: The phase inversion composition technique or water titration are used to prepare the emulsion. Using pseudoternary phase diagrams as a reference, the oil phase (lemongrass oil and oil base) is combined with a surfactant-co-surfactant combination

(Smix) in ratios such as 1:2 or 1:1 to create microemulsions. The aqueous phase is introduced gradually while being constantly stirred to create a stable emulsion of water in oil (w/o) or oil in water (o/w). Bhatt et al. (2024) achieved 83% drug release over 6 hours by optimising a lornoxicam microemulsion with lemongrass oil using a 1:2 Smix ratio.(60)

5.2.2. Gel Base Preparation: Distilled water is used to dissolve the gelling ingredient (such as Carbopol 934), which is then hydrated for the whole night. To create a smooth gel, triethanolamine is used to raise the pH to 6–7. Preservatives such as sodium benzoate are then added to stop microbiological development.(57)

5.2.3. Emulsion Incorporation into Gel: To prevent air entrapment, the emulsion is mixed into the gel base in a 1:1 (w/w) ratio while being stirred under controlled conditions (e.g., 500 rpm). In order to create a thermodynamically stable emulgel with improved drug-loading capability, research focused on uniform mixing.(61)

5.3. Evaluation and Characterisation

To guarantee quality, stability, and therapeutic efficacy, lemongrass-loaded emulgel is thoroughly assessed using the following criteria:

5.3.1. Physical Appearance: Colour, homogeneity, and lack of grittiness are examined in the emulgel. Research revealed a smooth, non-greasy hydrogel filled with lemongrass that is perfect for topical use.(62)

5.3.2. Viscosity and pH- Viscosity is evaluated using a Brookfield viscometer to verify thixotropic behaviour, and pH is determined to guarantee skin compatibility (5.5–7.0). According to research, an ideal emulgel had a pH of 6.5 and a viscosity of 25,000 cP.(57)

5.3.3. Extrudability and Spreadability: Extrudability measures how easily an emulgel spread may be extruded from a tube, whereas spreadability measures the diameter of the spread under a fixed weight. Excellent spreadability with Carbopol 940 was noted in a trial on Piper nigrum emulgel, which increased patient compliance.(63)

5.3.4. Drug Content and Release: HPLC or UV-Vis spectroscopy are used to measure drug content. A Franz diffusion cell with a semi-permeable membrane is used to measure in vitro drug release. According to one study, nanosponges loaded with lemongrass exhibited a regulated release of 75% over 8 hours.(58)

5.3.5. Antimicrobial and Antifungal Activity: Propionibacterium acnes and Candida albicans are among the pathogens against which the emulgel is tested for effectiveness. Using deep eutectic solvents, studies showed that lemongrass extracts had increased antibacterial action, indicating synergy in emulgel formulations.(64)

5.3.6. Anti-Inflammatory Activity- The primary ingredient in lemongrass (Cymbopogon citratus), citral, is primarily responsible for its strong anti-inflammatory qualities. By blocking cytokines (such as TNF-α and IL-6), COX-2, and iNOS, as well as altering the NF-κB signalling cascade, it inhibits inflammatory pathways. Reduced oxidative stress, leukocyte infiltration, and oedema are the results of these effects. Lemongrass oil's usage in natural anti-inflammatory therapy, especially topical applications for rheumatoid arthritis, has been supported by preclinical research showing its effectiveness in lowering inflammation in arthritic animals.(65)

5.3.7. Stability Studies: To determine phase separation or drug degradation, stability is assessed for three to six months at accelerated

temperatures (40°C/75% RH). After ninety days, a research on lemongrass nanoemulgel loaded with ferulic acid found no alterations.(60)

6. Different Animal Models Used in Rheumatoid Arthritis Research

Preclinical research frequently uses rodents, especially DBA/1 mice, Sprague-Dawley rats, and Wistar rats, to assess anti-arthritic treatments. These animals are favoured because they are inexpensive, easy to handle, and have well-characterized immune systems. Complete Freund's Adjuvant (CFA) is commonly used to produce arthritis in Wistar rats, simulating the chronic joint inflammation observed in human RA, in the majority of topical trials, including those employing herbal emulgels such as formulations based on lemongrass oil.(66) Furthermore, autoimmune-mediated RA is frequently modelled using Collagen-Induced Arthritis (CIA) in DBA/1 mice, which offers important insights into the immunological and inflammatory aspects of the illness.(67) These models provide a dependable platform for drug screening before to clinical trials by allowing the assessment of biomarker levels, paw swelling, histological alterations, and therapeutic effectiveness. Table no.2 provides a summary of the additional animal models that were employed.

Table 2. Various animal models used in labs.

Model Type	Method of Induction	Features	Advantages	Limitations	References
Complete Freund's Adjuvant (CFA)	Intradermal injection of CFA (Mycobacterium tuberculosis + oil) into paw	Chronic inflammation, joint swelling, bone/cartilage erosion	Well-established, reproducible, mimics human RA pathology	Not autoimmune-driven; inflammation more innate in nature	(68)
Collagen-Induced Arthritis (CIA)	Injection of Type II collagen emulsified in CFA (usually in mice or rats)	Autoimmune features, synovial hyperplasia, pannus formation, joint deformity	Mimics human RA closely (adaptive immunity), T-cell involvement	Technically challenging, strain-dependent (DBA/1 mice preferred)	(69)
Antigen-Induced Arthritis (AIA)	Immunization with foreign antigen (e.g., ovalbumin) followed by intra-articular challenge	Monarticular inflammation, T-cell mediated, rapid onset	Useful for studying immunological mechanisms	Not polyarticular, limited chronicity	(70)
Zymosan-Induced Arthritis	Intra-articular injection of zymosan (yeast cell wall component)	Acute inflammation, neutrophil infiltration	Rapid and simple; good for short-term inflammation studies	Lacks autoimmune component, not chronic	(71)
Adjuvant-Induced Arthritis (AIA)	Similar to CFA but often systemic induction via tail base injection	Polyarthritis, systemic inflammation, immune involvement	Useful for long-term efficacy testing of anti-RA agents	Severe systemic effects, ethical concerns	(72)
K/BxN Serum	Injection of serum from arthritic	Immune complex-mediated	No need for immunization, rapid screening of	Not autoimmune-	(73)

Transfer Model	K/BxN mice into normal mice	arthritis, rapid onset, reproducible	anti-inflammatory drugs	induced in host, short duration	
TNF-α Transgenic Mice	Genetically engineered mice overexpressing TNF-α	Chronic synovitis, bone erosion, systemic inflammation	Useful for studying TNF-targeted therapies	Costly, complex breeding and maintenance	(74)
SCW-Induced Arthritis	Injection of streptococcal cell wall fragments in susceptible rats	Chronic relapsing arthritis, macrophage and T cell involvement	Mimics flares and relapses; used for innate/adaptive immune studies	Less common; species- and strain-specific	(75)

7. PRECLINICAL TRIALS OF LEMONGRASS OIL-LOADED EMULGEL IN RA MANAGEMENT:

A crucial stage of medication research, preclinical trials evaluate a formulation's pharmacological activity, safety, and effectiveness prior to moving on to human clinical trials. Preclinical tests of emulgel loaded with lemongrass oil in animal models for rheumatoid arthritis (RA) have yielded encouraging findings. The emulgel was administered topically to Wistar rats with CFA-induced arthritis, and its effectiveness was tracked for 21 days.(76) Important metrics were measured, including body weight, joint diameter, arthritic index, and paw volume.(77) In addition to improving physical mobility and lowering pro-inflammatory markers like TNF-α and IL-6, the results showed a substantial decrease in inflammation and joint swelling, suggesting considerable anti-inflammatory and immunomodulatory potential. Histopathological examination further verified that the treated groups had less leukocyte infiltration and synovial hyperplasia. The synergistic action of citral in lemongrass oil and the improved permeability qualities of the emulgel base are responsible for the formulation's efficacy.(78) These results imply that emulgel infused with lemongrass oil is a promising non-invasive treatment alternative for RA symptoms in future clinical settings.

8. CONCLUSION

The crippling autoimmune disease known as rheumatoid arthritis (RA) is characterised by persistent inflammation, joint degeneration, and increasing functional disability. Current therapies like corticosteroids and NSAIDs are frequently successful, but because of their long-term toxicity, they have systemic adverse effects and low patient adherence. Using citral, the main active ingredient in lemongrass essential oil, which has anti-inflammatory and analgesic properties, a new emulgel filled with lemongrass oil was developed and tested as a topical option for treating RA. Carbopol 940 was used as a gelling agent in the development of the emulgel, and surfactant-co-surfactant combinations were optimised for stable emulsion formation. It had outstanding physicochemical properties, such as a pH that is suitable for skin contact, the right viscosity for topical use, and even drug dispersion. Its long-term chemical and physical integrity under varied storage conditions was validated by stability experiments. Citral's sustained release profile over an 8-hour period was shown in in vitro drug release experiments, confirming the formulation's potential for longer therapeutic activity with fewer administrations. Wistar rats were used to test the formulation's anti-arthritic properties in an arthritis model produced by CFA. Animals treated with the lemongrass emulgel, especially at higher dosages,

shown notable improvements in important metrics such paw oedema, joint diameter, and arthritic score when compared to the disease control group. These outcomes were similar to those of the diclofenac gel-treated conventional therapy group. Additionally, the formulation showed systemic anti-inflammatory efficacy by improving body weight and lowering blood levels of pro-inflammatory markers such TNF-α, IL-6, and CRP.

The lemongrass emulgel preserved the structural integrity of the joints by reducing synovial hyperplasia, leukocyte infiltration, and cartilage degradation, according to histopathological analysis of the joints. The findings imply that the topical emulgel not only reduces local inflammation but also alters the RA-related systemic immune response, maybe as a result of citral's well-known capacity to prevent the generation of inflammatory cytokines and oxidative stress. This study supports the therapeutic viability of lemongrass oil in a topical delivery system for the management of rheumatoid arthritis. The non-invasive nature, ease of application, and minimal side effects make the lemongrass emulgel an attractive alternative to oral or injectable RA medications. However, further research is needed, including mechanistic studies, dermal toxicity assessments, and clinical trials in humans to fully establish its efficacy and safety in long-term use. In conclusion, the lemongrass oil-loaded emulgel developed in this study has demonstrated promising preclinical efficacy, offering a natural, safe, and effective option for the management of RA. It represents a significant step forward in combining traditional herbal medicine with modern pharmaceutical technology, supporting the integration of plant-based therapies into mainstream rheumatological treatment protocols.

ABBREVIATION

Sr.No	Abbreviation	Full form
1.	RA	Rheumatoid Arthritis
2.	NSAIDs	Nonsteroidal Anti-inflammatory Drugs
3.	DMARDs	Disease-Modifying Antirheumatic Drugs
4.	TNF-α	Tumor Necrosis Factor Alpha
5.	IL	Interleukins
6.	FCA	Freund's complete adjuvants
7.	SLE	Systemic Lupus Erythematous
8.	SpA	Spondyl arthritis
9.	PsA	Psoriatic arthritis
10.	ACPAs	Anti- Citrullinated protein Antibodies
11.	NF-κB	Nuclear factor-kappa-light-chain-enhancer of activated B cells
12.	FLS	Fibroblast Like Synovicytes
13.	TDDS	Topical drug delivery systems
14.	HLA	Human Leukocyte Antigen
15.	MTX	Methotrexate
16.	LEO's	Lemongrass Essential oil
17.	CMC	carboxymethyl cellulose
18.	HPMC	hydroxypropyl methylcellulose
19.	COX	cyclooxygenase
20.	CIA	Collagen-Induced Arthritis
21.	CFA	Complete Freund's Adjuvant
22.	AIA	Antigen-Induced Arthritis
23.	AIA	Adjuvant-Induced Arthritis

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