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Original Article

Formulation and Evaluation of Polyherbal Pain Relief Gel for its Effect on Rheumatoid Arthritis

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ABSTRACT

Background: Almost 1-3% of people worldwide suffer from arthritis. It is an autoimmune disease that can harm extra-articular organs in addition to joints. Rheumatoid arthritis is commonly treated with steroidal, non-steroidal anti-inflammatory, disease-modifying, antirheumatic, and immunosuppressive medications. These medications have the potential to cause several kinds of side effects, such as gastrointestinal issues, immunodeficiency, and humoral changes. Ayurvedic and Siddha medicine have been recognised as alternative treatments for arthritis. This study aims to develop a topical poly-herbal gel (containing extracts of ginger, garlic, clove, and eucalyptus) and evaluate it, as well as determine its ability to reduce inflammation in animals. The essential oils from the herbs were extracted using the hydro distillation method. **Materials and Methods:** To prepare the poly-herbal gel, PEG 400, Carbopol 934, and the appropriate amount of distilled water have been used. After the herbal extract and gelling part were properly mixed. The final formulation's pH was adjusted using triethanolamine. **Results:** Various physical tests were conducted on the produced gel like colour, appearance, pH, texture, and viscosity as well as primary skin irritation, analgesic, and anti-inflammatory tests in rats to be compared to the marketed product. The study observed that carrageenan significantly enhanced paw oedema and cellular infiltrates, whereas the test sample (a polyherbal gel including ginger, garlic, eucalyptus, and clove extract) significantly decreased paw oedema. **Conclusion:** In the treatment of rheumatoid arthritis, the developed topical polyherbal gel may be a safe and effective alternative for non-steroidal anti-inflammatory medicines; however, further study is required.

Keywords: Anti-inflammatory agent, Herbal therapy, Rheumatoid arthritis, Topical formulation.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic inflammatory condition that affects extra-articular organs such as the kidney, heart, digestive system, lungs, skin, eyes and nervous system, as well as joints and the immune system (Conforti *et al*., 2021), (Cojocaru *et al*., 2010). RA affects 1-3% of the population, with a female predominance of 3:1 that decreases with age. This condition appears to have a genetic basis. RA is defined by the gradual and permanent deterioration of the synovial-lined joints, resulting in joint function loss and deformity. The usual degradation in bone, tendons, ligaments, and cartilage is caused by extracellular matrix degradation, another characteristic of RA (Grassi *et al*., 1998). Although there is no precise cure for arthritis, treatments can help with this condition: Medication (which targets the immune system's inflammatory response), Physical Therapy (which can assist in increasing strength, range of motion, and general mobility), and Therapeutic Injections. However, therapy with drugs may be accompanied by significant side effects and is costly (Lindler *et al*., 2020). Rheumatoid arthritis is often treated with three types of medications: Nonsteroidal Anti-Inflammatory Medicines (NSAIDs), corticosteroids, and drugs called Disease-Modifying Antirheumatic Drugs (DMARDs). While DMARDs might take weeks or months to provide clinical results, NSAIDs and corticosteroids work rapidly. So alternative treatments have been under investigation.

Herbal products have shown promise towards the safe and efficient treatment of arthritis. We have selected four herbs (ginger, garlic, clove, and eucalyptus) that can help to treat rheumatoid arthritis symptoms, pain, and inflammation. Ginger (*Zingiber officinale)* is a member of the *Zingiberaceae* family (Kumar *et al*., 2013). It was shown that 6-gingerol present in ginger significantly reduced lysosomal enzyme levels while inhibiting lactate dehydrogenase and acid phosphatase (Al-Nahain *et al*., 2014). In addition to showing strong anti-inflammatory properties, it also shows anti-oxidant activity and is effective in treating nausea and chronic indigestion. Gingerol has been shown to inhibit tumour promotion and induce apoptosis in cancer cells (Sharma *et al*., 2023). Garlic (*Allium sativum*) belongs to the family *Alliaceae*

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(Ammarellou *et al.*, 2022). It contains sulphur compounds, including diallyl sulphide, S-allylmercaptocysteine, and ajoene, which suppress the inflammatory factor NF-κB. (Aggarwal and Shishodia, 2004). Garlic lowers blood pressure and cholesterol levels, decreasing the risk of coronary heart disease (Chan *et al.*, 2013). It has antibacterial, antifungal, and antiparasitic properties, which assist in the treatment of infections (Tesfaye, 2021). Clove (*Syzygium aromaticum*) is a member of the *Myrtaceae* family (Cortés-Rojas *et al.*, 2014a). Eugenol (4-allyl-2-methoxyphenol) is a major phenolic compound found in Clove and it has anti-inflammatory properties (Kim *et al.*, 2003)which could be due to its ability to block the Nuclear Factor-Kappa B (NF-κB) signalling pathway (Zhang *et al.*, 2013). Clove has strong antioxidant properties and remarkable antibacterial effectiveness, working against a wide range of bacterial and fungal species (Cortés-Rojas *et al.*, 2014b).

Eucalyptus *(Eucalyptus globulus Labill)* belongs to the family *Myrtaceae* (Abdel-Massih and El Beyrouthy, 2022). It contains 1,8-cineole (synonym: eucalyptol), which shows local hyperaemic and anti-inflammatory properties (Juergens, 2014). The herbs possess strong anti-inflammatory and antioxidant properties, which aid in reducing inflammation and tissue damage. It also has antibacterial, antiviral, and antifungal properties (Sadlon and Lamson, 2010). In the present study, we developed a pain relief gel and conducted a comparative study with the marketed product to demonstrate its anti-inflammatory activity. Under normal storage conditions, the herbal preparation remained stable. There was no oedema, erythema, or skin irritation after the gel was applied to the skin for around 72 hrs testing. Although these herbs have the potential to treat rheumatoid arthritis, more study is needed to assess their safety, effectiveness, bioactivity, and optimal bioavailability.

MATERIALS AND METHODS

The mature fresh Ginger, Garlic, Clove, and Eucalyptus herbs were collected from a local nursery (B.K. Roy Nursery, Pallyshree, Arambagh). Carbopol 934 was purchased from Loba Chemie Pvt. Ltd., Polyethylene glycol and Triethanolamine were purchased from Merck Specialities Pvt. Ltd., EDTA was purchased from Loba Chemie Pvt. Ltd., Menthol and Camphor supplied from Qualikems Pvt. Ltd., and Sunset Yellow, Brilliant Blue, Cochineal Colouring agent supplied by Sigma-Aldrich.

Extraction of oil from Ginger, Garlic, and Clove: All the herbal extract was obtained using the Clevenger apparatus through hydro distillation technique. Hydro Distillation (HD) is a conventional process for extracting essential oils; it employs water as a solvent, which has the benefit of not leaving hazardous residues at the completion of the extraction (Sohpal, 2018).

Method of Preparation of Gel base

To prepare the gel base, different amounts of Carbopol 934 were used. 50 mL of distilled water was taken to dissolve the accurately weighted Carbopol. After the Carbopol dispersed properly, it was kept aside to swell. Using a mechanical stirrer, it was stirred for about 30 min. Then P.E.G 400 and EDTA were added with constant stirring. After that add distilled water to make up the final volume 100 mL. Tri ethanol amine was added in different amounts to the formulation batches to get the accurate pH of the gel formulations as given in Table 1. It was found that Formulation batch F3 shows the promised viscosity as well as pH, so we finalised formulation batch F3 to prepare the herbal gel.

Preparation of Herbal Gel: 0.25 mL herbal extract from each herb was added to the previously prepared gel base (formulation batch F3) and stirred to mixed homogeneously for a sufficient time period. After the proper mixing of gel base and herbal extract, camphor and menthol were added to the formulation for a cooling sensation. Three different Colouring agents have been used as shown in Table 2. to check the appearance of the gel. Collapsible tubes were used to store the prepared gel for evaluation purposes.

Evaluation of Gel

Organoleptic characteristics

Physical parameters like colour, appearance and feel on the application were recorded.

pH

A calibrated digital pH meter was used to determine the pH of herbal gels.

Viscosity

Using a Brookfield viscometer RVT, with spindle no 7, the gel's viscosity was measured (GIRI and BHALKE, 2019).

Table 1: Gel base Formulation.

Ingredients	F1	F2	F3	F4	F5
Carbopol 934 (g)	0.5	1.0	1.5	2.0	2.5
Triethanolamine (mL)	1.0	0.75	0.5	0.25	0.0
Polyethylene Glycol 400 (mL)	5.0	5.0	5.0	5.0	5.0
EDTA (mg)	5.0	5.0	5.0	5.0	5.0

Extrudability

A narrow collapsible tube containing roughly 20 g of gel was firmly pushed at the crimped end to conduct this test, and a clamp was used to keep the tube from rolling back. After the cap was taken off, the gel was extruded. Weighing and measuring the amount of extruded gel (Rajasekaran *et al*., 2016).

Spreadability

The apparatus used to measure spreadability was a wooden block with a pulley on one end. By examining gel slip and drag characteristics, the aforementioned method determined spreadability. For this ground slide, an excessive amount of gel (roughly 2 g) was applied. Subsequently, the gel was fixed with a hook and positioned between this glass slide and another one of the same sizes as the stationary ground slide. A 1 kg weighted plate was put on top of the two slides for 5 min to eliminate air and create a uniform gel coating between them. The excess gel was scraped off the edges. After that, the top was pulled at 80 g. Lastly, using the string attached to the hook, the duration required for the top slide to move 7.5 cm was recorded (Jadhav *et al*., 2010).

Homogeneity

After being put in the container, all hydrogels were visually examined for homogeneity. They were inspected for appearance and the presence of any aggregates (Dwivedi and Gupta, 2012).

Stability Study

A stability study is essential to evaluate the physical, chemical, and microbiological stability of a gel formulation under various environmental conditions over a specific period. It ensures the product's efficacy, safety, and shelf life. The stability study of the prepared gel was done by following ICH Q1 guidelines. To examine the gel's appearance, pH, and spreadability, it was kept in collapsible tubes for three months at Accelerated Conditions i.e. 40±2°C/75±5% RH (Khagga *et al*., 2019).

Skin irritation test

The skin irritation test evaluates the potential of a gel formulation to cause adverse skin reactions, such as redness, swelling, or erythema. The test involves applying a small amount of the gel (approximately 0.5 g) to a shaved area on the dorsal skin of albino rats, ensuring the site is free of cuts or abrasions. The area is either left uncovered or covered with a patch for 24 hr. After the exposure period, the application site is inspected at intervals (e.g., 1, 24, and 48 hr) for signs of irritation using a scoring system, such as the Draize scale, where redness and edema are rated from 0 (no reaction) to 4 (severe reaction). A lack of significant redness or swelling indicates that the gel is non-irritating and safe for topical use. According to OECD 404, skin irritation tests are used to establish if a product or substance would irritate human skin when in touch with it. This test is required to ensure the product's safety before it is utilised on the human body.

Selection and handling of animals

In the present study, healthy male and female albino rats weighing 120-150 g were used as experimental animals. The experiment was carried out at Calcutta School of Tropical Medicine, Chittaranjan Avenue, Calcutta-700 073, West Bengal (Registration No: 681/GO/Re/S/2002/CPCSEA). The animals were housed together in a clean tank, which was large enough to allow free movement of the animals and accommodations for holding drinking water and feeding. The room temperature was 25°C±30°C, the humidity was 45-55%, and the light period was 12 hr (6.00 A.M to 6.00 P.M). Animals were fed commercially available food and filtered tap water. The day before the experiment, Wister albino rats had their dorsal hairs trimmed. Rats were separated into two groups. Group 1 served as the control, with a simple gel base. Group 2 received the gel formulation. The developed gel was evaluated for skin irritation, and no erythema or oedema were found in any of the formulations, throughout the 72 hrs of testing (Prakash *et al*., 2010).

Table 2: Herbal Gel Formulation.

Formulation Batch	G1	G2	G3	G4
Carbopol (g)	1.5	1.5	1.5	1.5
Tri -Ethanol amine (mL)	1.5	1.5	1.5	1.5
Polyethylene Glycol 400 (mL)	5	5	5	5
EDTA (mg)	5	5	5	5
Ginger oil (mL)	NA	0.25	0.25	0.25
Garlic oil (mL)	NA	0.25	0.25	0.25
Clove oil (mL)	NA	0.25	0.25	0.25
Eucalyptus oil (mL)	NA	0.25	0.25	0.25
Camphor (g)	1	1	1	1
Menthol (g)	2.5	2.5	2.5	2.5
Colouring agent	NA	Sunset Yellow	Brilliant blue	Cochineal

Anti-inflammatory effect against carrageenan-induced paw oedema

A popular approach to determining anti-inflammatory drugs is to test their ability to reduce oedema in rats' hind paws after phlogistic agent injection. Brewer's yeast, formaldehyde, dextran, albumin, kaolin, aerosil®, and sulphated polysaccharides such as carrageenan or formalin are examples of phlogistic agents (irritants). There are several ways to measure the effect. Before and after the irritant is applied, the injected paw volume is typically measured, and the results are compared with the controls (Vogel and Vogel, 2008). Oedema is the initial stage of inflammation. The most widely used model to evaluate the anti-inflammatory effects of new medications is paw oedema induced by carrageenan.

Method of selection of different groups

Wister albino rats are the experimental animals. Three groups of 6 animals each were created out of the 18 total. Three groups of animals experimented with Control, Standard and Test Formulation. Group I-Control: Gel base only (Topical), Group II-Standard: Diclofenac sodium gel (Topical) and Group III-Test: Gel formulation (Topical).

Study Procedure

About 120-150 g body weight male or female rats were used and animals were identified using picric acid. Then the left hind paw volume (initial volume) was measured with a vernier calliper and documented. The rats received a subcutaneous injection of 0.1 mL of 1% carrageenan solution on the plantar side of their left hind paw as shown in Figure 1. After 2 hrs, 1 g of test sample and diclofenac gel were smoothly applied to the planter side of the left hind paw of Group III and Group II rats. The paw volumes of all animals were measured with a vernier calliper after injection and 0, 1, 3, 6, 12, and 24 hrs. of test samples and standard drugs as shown in Figure 1, in addition to comparing to the control group.

The collected data were statistically analysed using the ANOVA (Analysis of Variance) test.

RESULTS

The prepared polyherbal pain relief gel formulation was assessed for its macroscopic characteristics and qualities such as color, aspect, and aroma. All the gel formulations have a smooth texture and homogeneous and characteristic odour of oil extracted from different herbs. Three different colours Sunset Yellow, Brilliant Blue and Dark pink give the gel formulations an attractive and homogenous appearance. The physical parameters which were evaluated are shown in Table 3. The pH of the gel formulation lies between 58-5.9 and did not produce any skin irritation. Viscosity was found to be 4675 cps for G2 formulation, 4715 cps for G3 formulation and 4686 cps for G4. The spreadability of all formulations is found satisfactory as it has high values with low spreading time. The parameters of viscosity and spreadability for all the formulations is given below in Table 3. From the extrudability study, it has been found that nearly 93 to 95% of the gel extruded from the collapsible tube. The initial weight of the formulation was between 19.96-20.25 g and the wight of the extruded gel was 18.6-19.02 g which represents a good characteristic of the gel. After performing the skin irritation test shown in Figure 2, no erythema or oedema were found in any of the formulations, throughout the 72 hrs. of testing, indicating that the developed gel formulation is safe.

Stability Studies for 3 months at Accelerated Conditions

The Accelerated stability study of Gel formulation was done as per ICH Q1 guidelines for accelerated conditions (40°C±2°C/75%±5% RH for 3 months). After performing the stability study, all the gel formulations were found smooth in appearance. The spreadability was 19.4, 20.3,19.7 for G2, G3 and G4 batches accordingly. The pH was found between 5.76-5.81.

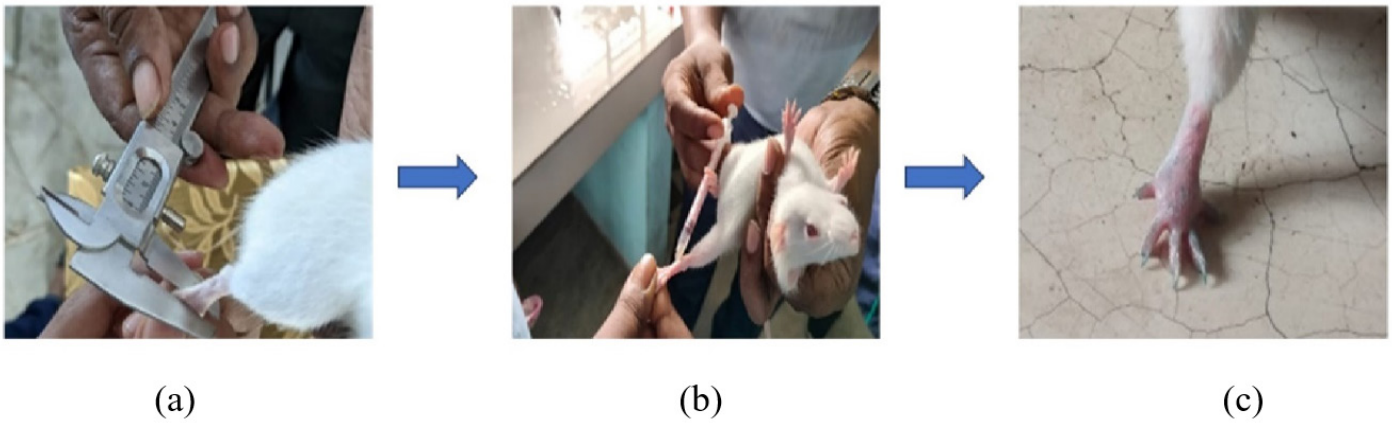

Figure 1: (a) Initial measurement of Rat Paw Volume using Vernier Callipers, (b) Subcutaneous injection of 0.1 mL of 1% carrageenan solution on the plantar side of their left hind paw, (c) Inflammation induced in the rat paw.

Skin irritation test in rat model

Anti-phlogistic effect of gel formulation on Carrageenan-induced oedema in rats

Carrageenan was injected intraperitoneally into the hind paw, causing a progressive rise in oedema paw volume in the control group. The reference medicine, diclofenac sodium gel, significantly decreased the paw oedema. The test sample (poly herbal gel containing ginger, garlic, eucalyptus, clove extract) significantly reduced oedema formation in rat paw 3 hrs. after carrageenan inject shown in Table 4. It was observed that the paw volume was respectively decreased after 3 hrs., 6 hrs., 12 hrs., and 24 hrs. by the standard drug and the test sample. Which shows the potential of the polyherbal pain relief gel to reduce the inflammation.

Table 4 presents the rat paw volume measurements subsequent to Carrageenan-induced edema along with treatment using control, standard (diclofenac sodium gel), and test (polyherbal gel) preparations at different time intervals (0, 1, 3, 6, 12, and 24 hrs.). The control group exhibited a gradual increase in paw volume, peaking at 24 hrs. (0.82±0.006 ml). The standard formulation markedly restricted this increase, with paw volume attaining only 0.65±0.006 ml at 24 hrs. The test formulation exhibited significant anti-inflammatory activity, sustaining a paw volume of 0.65±0.006 ml at 24 hrs, closely resembling the standard. Both

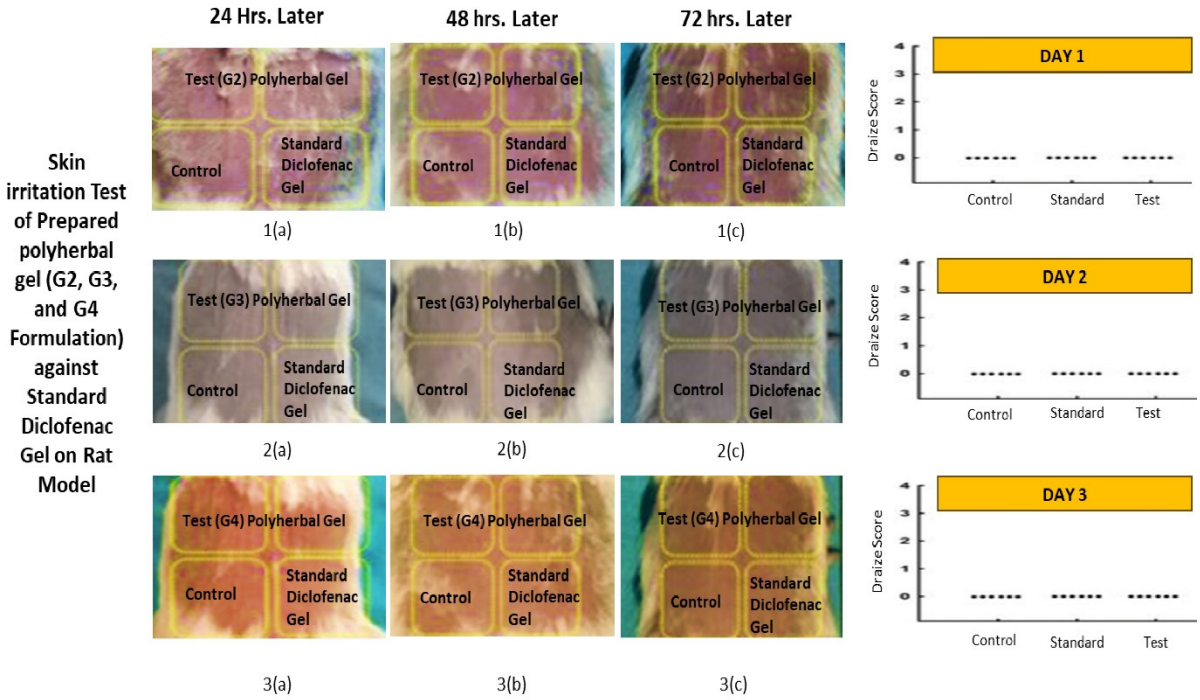

Figure 2: Skin Irritation Test on Rat Model. 1(a) Control, Standard and G2 formulation after 24 hrs. study showed "0" Scoring which means no irritation occurs. Similar results for 1(b) and 1(c) after 48 hrs. and 72 hrs., respectively. 2(a) Control, Standard and G3 formulation after 24 hrs. study showed "0" Scoring which means no irritation occurs. Similar results for 2(b) and 2(c) after 48 hrs and 72 hrs, respectively. 3(a) Control, Standard and G4 formulation after 24 hr. Study showed "0" Scoring which means no irritation occurs. Similar results for 3(b) and 3(c) after 48 hrs and 72 hrs, respectively.

Table 3: Physical Evaluation of Gel Formulation.

2	Colour	Appearance	Feeling	pH	Viscosity (cps)	Spreadability (gm. cm/sec)
G2	Sunset yellow	Homogeneous	Soothing effect	5.9	4675	20.19
G3	Brilliant blue	Homogeneous	Soothing effect	5.8	4715	21.16
G4	Dark Pink	Homogeneous	Soothing effect	5.9	4686	20.19

Table 4: Measurement of Rat Paw volume after treatment with Control, Standard and Test Formulation after 1, 3, 6, 12 and 24 hr.

Group	0	1 hr	3 hrs.	6 hrs.	12 hrs.	24 hrs.
Control	0.46±0.006	0.49±0.006	0.64±0.006	0.73±0.006	0.72±0.006	0.82±0.006
Standard	0.45±0.006	0.47±0.006	0.52±0.006	0.58±0.006	0.62±0.006	0.65±0.006
Test	0.46±0.006	0.47±0.006	0.53±0.006	0.62±0.006	0.63±0.006	0.65±0.006

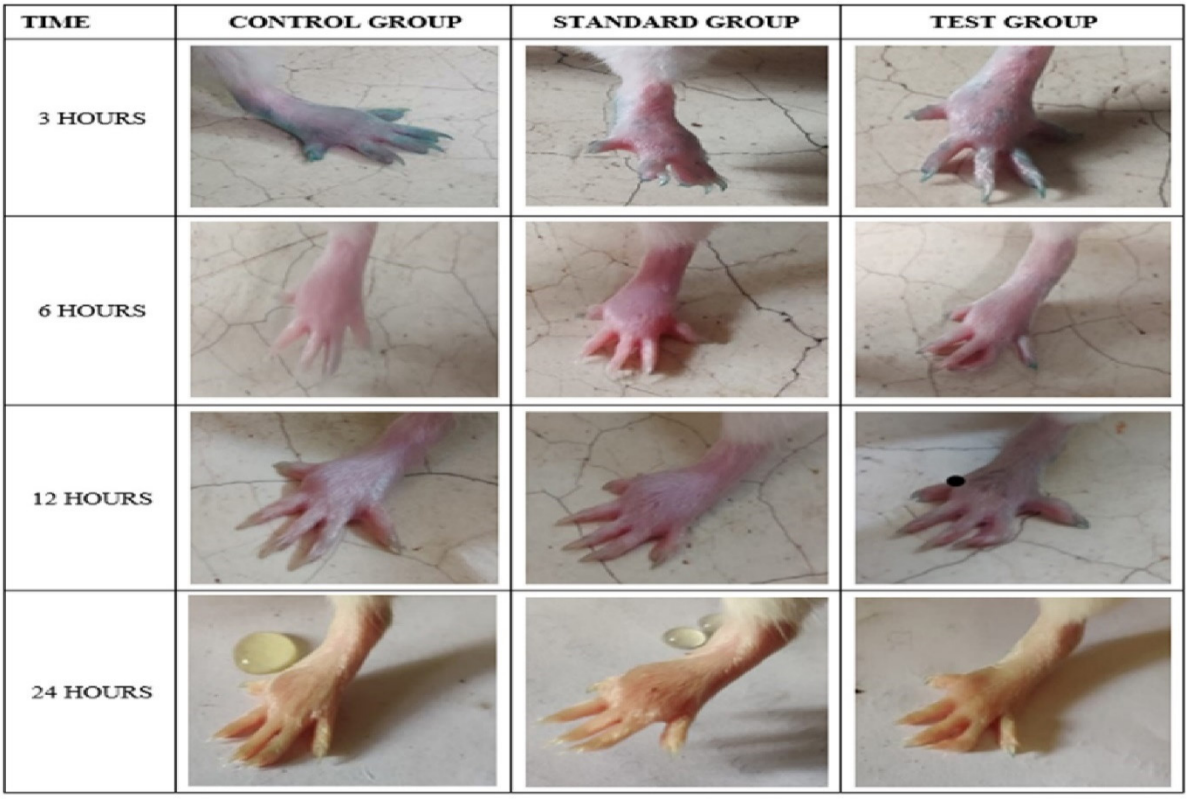

Figure 3: Effect of standard and the test gel formulation on Carrageenan-induced oedema in rats after 3 hr, 6 hr, 12 hr, 24 hr.

the test and standard groups demonstrated diminished oedema formation as early as 3 hrs post-injection, with the standard group initially surpassing the test group, but both groups converged by the 24 hrs mark as presented in the Figure 3. The results demonstrate the effectiveness of the polyherbal gel in alleviating inflammatory swelling, indicating its performance is comparable to that of diclofenac sodium gel in reducing Carrageenan-induced inflammation.

DISCUSSION

The present study aims to prepare a topical polyherbal pain relief gel using natural compounds to treat Rheumatoid Arthritis (RA) more safely than marketed products by reducing the common side effects. The selected herbs (Ginger, Garlic, Clove, and Eucalyptus) show their potential against RA. Ginger contains secondary metabolites, particularly gingerols, which have anti-inflammatory properties (Funk *et al.*, 2016). Garlic also significantly reduced pain intensity and tender joint counts in RA patients (Moosavian *et al.*, 2020). Clove suppresses the RA by inhibiting the Nuclear Factor-Kappa B (NF-κB) signalling pathway, a critical regulator of inflammatory responses (Shakeel *et al.*, 2021). Eucalyptus oil contains compounds such as 1,8-cineole, which has been found to have anti-inflammatory properties. Studies show that this compound may decrease cytokine secretion from T-lymphocytes, lowering inflammation and pain associated with conditions like RA (Jun *et al.*, 2013). Combining these herbs produces synergistic effects and enhanced therapeutic efficacy. Different concentrations of gelling agent i.e. Carbopol 934 polymer were taken to optimize the formulation. The prepared gel formulation has a smooth texture and soothing effect. The viscosity of the gel was found to be sufficiently consistent in its shape and feels slippery and smooth on touch. The produced gels meet the optimal quality for topical administration and have adequate spreadability to aid in the even distribution of this gel to the surface of the skin. The spread of gels determines their therapeutic efficacy. The extrudability of all the formulations was found satisfying. All the gel formulations were found smooth in appearance after performing the stability study. Skin irritation study ensured that the prepared gel formulations were free from skin irritation or sensitization, and they did not have any edema. The prepared gel formulation shows its anti-inflammatory potential by significantly reducing edema formation in rat paws 3 hr after carrageenan injection compared to the marketed product. While using Diclofenac sodium gel, various adverse effects occurred, such as burning, itching, redness, skin rash, swelling, or discomfort at the application site, irritating skin, itchy or burning eyes, eye pain, and headaches, especially migraines. Skin redness, eye swelling or redness, soreness or pain around the eyes and cheeks, and heightened sensitivity to sunlight (Alfaro and Davis, 2023). Diclofenac tablets and capsules can cause stomach or gut ulcers if taken for a long period of time or in high doses (Boelsterli, 2003). If it takes large amounts over an extended period, it causes a tiny chance of developing heart or renal failure (Dhanvijay *et al.*, 2013; McGettigan and Henry, 2013). On the

other hand, hydro herbal gels are topically formulated with natural ingredients derived from plants, such as herbs (Ginger, Garlic, Clove, and Eucalyptus etc.) By reducing inflammation, these ingredients can help alleviate pain associated with conditions such as arthritis, muscle strains, or joint stiffness. Herbal gels may have a calming or soothing effect on the body. Ingredients like clove and eucalyptus can provide a pleasant fragrance and promote relaxation That's why these ingredients are often considered safer and gentler on the body compared to synthetic chemicals found in conventional pain relief products. We can use this formulation to avoid side effects for long-term medication. The research illustrates the considerable anti-inflammatory efficacy of a polyherbal gel comprising ginger, garlic, eucalyptus, and clove extracts in alleviating Carrageenan-induced paw edema in rats. The test gel significantly diminished oedema starting at 3 hrs post-injection, with persistent effects noted at 6, 12, and 24 hrs, corresponding to the standard diclofenac sodium gel. This effect is due to the bioactive substances in the herbal ingredients, including gingerols, allicin, eucalyptol, and eugenol, that suppress inflammatory mediators such as prostaglandins and cytokines. The polyherbal gel's efficacy comparable to a synthetic NSAID indicates that it could serve as a safer, natural approach for inflammation management, with diminished possibility of systemic complications. These results underscore the gel's potential for addressing inflammatory conditions, necessitating additional clinical assessment.

CONCLUSION

Topical drug delivery systems have emerged as an effective approach in recent years, due to their ability to promote patient adherence. Natural remedies are especially popular since they are generally considered safer and have fewer side effects than synthetic drugs. Furthermore, herbal products have advantages such as biocompatibility, ease of availability, and a lower risk of causing allergic responses. As a result, they show great potential in treating a variety of dermatological and systemic disorders by topical treatment. In the present study, we developed a polyherbal gel to assessed the combined action of ginger, garlic, clove, and eucalyptus oil for managing rheumatoid arthritis symptoms, such as reduced inflammation, pain, and stiffness. By doing the comparative study of our optimized hydro gel formulation with marketed product Diclofenac gel, it has been found that the better efficacy has been observed with our optimized formulation in Wister rat after performing Carrageenan induced paw oedema with both the samples of our Formulation (F3) and marketed product. All other parameter of Hydrogel (pH, viscosity, spreadibility, extrudability, homogeneity) has been found satisfactory with F3 formulation thus we can conclude that F3 formulation is most robust formulation and showing better efficacy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

The animal experiment was carried out at Calcutta School of Tropical Medicine, Chittaranjan Avenue, Calcutta-700 073, West Bengal (Registration No: 681/GO/Re/S/2002/C PCSEA). The approval is taken from the Animal Ethical Committee of the Institute.

AUTHOR'S CONTRIBUTION

Investigation, Drafting and editing: Bratati Bandyopadhyay; Data collection and writing: Arif Munsi; Animal Study: Kabirul Islam Mollah; Conceptualization, supervision, and final editing: Biplab Debnath; Data curation and experimental work: Amlan Bishal; Final approval: All authors.

ABBREVIATIONS

RA: Rheumatoid Arthritis; **OECD:** Organization for Economic Co-operation and Development; **PEG:** Polyethylene Glycol; **NSAIDs:** Non-steroidal anti-inflammatory drugs; **DMARDs:** Disease-modifying anti-rheumatic drugs; **EDTA:** Ethylenediaminetetraacetic acid; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **ANOVA:** Analysis of Variance.

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