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Original Article

Formulation and Evaluation of Novel Multi Herbal Gel for the Management of Pain and Inflammation

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ABSTRACT

Herbal medication is impacting 75–80% of the global population, especially in developing nations, due to affordability and fewer adverse effects. The WHO states herbal remedies are used 2-3 times more than allopathic treatments. Herbal remedies are becoming more popular due to cultural acceptance, accessibility, and cheaper costs. Synergistic effects from whole plants may boost efficacy and reduce toxicity in herbal therapy. However, many herbal products are unlicensed and untested for safety and efficacy. Herbal sales are estimated at $250 billion worldwide. This study used Terminalia arjuna and Annona squamosa extracts to develop a polyherbal gel for pain and inflammation. The gel formulation was tested for physical and chemical stability, maximizing viscosity and spreadability. Herbal extracts were Soxhlet extracted, and Carbopol 934 and other excipients formed the gel base. The formulated herbal gels were further evaluated for different parameters. As per the records in literature review for the activity of Terminalia arjuna and Annona squamosa in pain management the developed herbal gel formulation could proposes a possible technique to use the before mentioned herbs for the management of pain and inflammation.

Keywords: *Herbal Medicine; Topical Gel; Pain Management; Inflammation; Terminalia arjuna; Annona squamosa.*

Introduction

In recent years, the Siddha and Ayurvedic medical systems have garnered acknowledgment as alternate methods for the management of pain and inflammation. These conventional systems prioritize natural cures and holistic therapies. Two plants typically employed in these traditions for the treatment of arthritis are Annona squamosa (usually referred to as custard apple) and Terminalia arjuna (known as the arjuna tree). Integrating Annona squamosa and Terminalia arjuna into arthritis management offers a supplementary strategy to traditional therapies. These conventional remedies provide possible advantages with reduced adverse effects, rendering them a significant choice for persons pursuing therapies for arthritis. The effectiveness and safety of these plants in treating this difficult condition are still being studied as interest in holistic and natural therapies increases [1].

Annona squamosa, or custard apple, has a longstanding application in Indian medicine for addressing numerous ailments, including inflammation and rheumatism [2]. Studies have shown that the

ethanol extract of this plant can suppress the production of COX-2, TNF-α, and iNOS in RAW264.7 cells activated by lipopolysaccharide (LPS), highlighting its anti-inflammatory characteristics.

Pharmacological research indicates that Annona squamosa exhibits multiple therapeutic benefits, including analgesic and vasodepressant properties [3]. It also demonstrates antipyretic actions against yeast-induced fever in rats, antimalarial characteristics, and antioxidant activities. Additionally, it has demonstrated anti-ulcer efficacy against ethanol-induced stomach ulcers in rats [4]. Moreover, Annona squamosa has been shown to inhibit the synthesis of TNF-α and nitric oxide in human peripheral blood mononuclear cells [5]. Numerous chemicals have been extracted from Annona squamosa, such as arachidic acid, apigenin, apigenin-7-O-glucuronide, chrysoeriol-7-O-glucuronide, and luteolin-7-O-glucuronide. Annona squamosa possesses anti-inflammatory and analgesic effects, rendering it advantageous for mitigating arthritis symptoms. The fruit and leaves possess several phytochemicals, including as flavonoids and alkaloids, that enhance its medicinal properties. Traditional practitioners utilize extracts from the leaves and fruit to alleviate swelling and pain related to arthritis. Moreover, its antioxidant qualities may mitigate oxidative stress, hence enhancing joint health [6].

Terminalia arjuna, referred to as Arjuna, is esteemed in Siddha and Ayurveda medicine, chiefly for its cardiovascular advantages. Nonetheless, its anti-inflammatory characteristics render it a valuable therapeutic alternative for arthritis [7].

Cardiovascular Advantages: Terminalia arjuna has been thoroughly researched for its capacity to enhance cardiovascular health. Clinical research demonstrates that its bark extract may decrease blood pressure, lower cholesterol levels, and enhance overall cardiac function. The advantages are ascribed to the existence of active substances, including flavonoids and tannins, which enhance cardiovascular health.

The bark of Terminalia arjuna possesses anti-inflammatory properties. Pharmacological research has shown that bark extracts can suppress pro-inflammatory cytokines, hence reducing inflammation in joint tissues. This technique can be especially advantageous for people with arthritis, where joint inflammation is a major issue.

Enhancement of Joint Function: Terminalia arjuna is frequently used in herbal preparations designed to enhance joint function. Clinical research indicates that its anti-inflammatory characteristics may mitigate pain and stiffness related to arthritis, hence improving the overall quality of life for patients.

Circulatory Enhancement: Terminalia arjuna is purported to improve circulation in herbal therapy. Enhanced blood circulation can assist in the transportation of nutrients to injured joints and tissues, promoting rehabilitation and alleviating pain.

The bark extract is believed to enhance the integrity of connective tissues. This feature may enhance joint stability and integrity, hence mitigating arthritic symptoms.

Terminalia arjuna serves as a significant natural treatment for arthritis management. The amalgamation of cardiovascular advantages, anti-inflammatory characteristics, and capacity to improve joint functionality renders it a prominent subject of clinical and pharmacological investigation within traditional medicinal frameworks. With the increasing interest in natural and holistic therapies, the usefulness of Terminalia arjuna in the therapy of arthritis is expected to be further investigated and substantiated.

No previous research has been conducted on the preclinical trials of Annona squamosa and Terminalia arjuna in relation to a topical gel for anti-arthritic action [8,9]. A topical herbal gel was formulated with extracts from Annona squamosa and Terminalia arjuna and assessed for its anti-arthritic properties. This research seeks to furnish empirical evidence endorsing the conventional application of these plants in the treatment of arthritis.[6]

The gel formulation presents multiple benefits: it is simple to use, delivers a targeted action, and induces minimum discomfort or irritation during application. Moreover, topical treatment circumvents the first-pass metabolism linked to oral drugs, so reducing gastrointestinal degradation and facilitating direct transport to the targeted location.

All components of Annona squamosa and Terminalia arjuna are exploited for medicinal purposes, with the leaves predominantly used in traditional medicine to treat arthritis. Consequently, the topical gel formulation was formulated using the whole leaf extract and further evaluated for different parameters.

Material and Methods

The mature fresh bark Annona squamosa and Terminalia Arjuna were collected from natural

remedies medicinal garden at ordinance factory, Rajgir, Nalanda, Bihar. Methanol, petroleum ether, carbopol 934, triethanol amine, disodium EDTA, propylene glycol and DM water provided by Nibha Institute of Pharmaceutical Sciences, Rajgir.

Preparation of Extracts

The leaves of Annona squamosa and Terminalia arjuna were meticulously handled to remove dirt and residual substances, following a comprehensive cleaning and shade drying. The coarse powdered bark of Terminalia arjuna was extracted using a Soxhlet extractor with methanol for 72 hours. The coarse powdered bark of Annona squamosa was extracted using a cold maceration process with methanol for a duration of 7 days. Following extraction, both solutions were filtered and concentrated utilizing an IKA Rotary Evaporator (Model No RN 10 Digital V, ILMAC Germany) at a temperature of 40°C [10]. The concentrated extracts were thereafter kept at 4-8 °C for future utilization.

Preparation of Gel Base

Carbopol 934 was dissolved slowly with stirring in 60 mL of demineralized water for 1 h to avoid agglomeration Then disodium edetate and triethanolamine were dissolved in 10 mL of demineralized water separately and stirred for 10 min. Mixed 4.83 mL of propylene glycol in 12 mL of demineralized water with stirring for 10 min. Disodium edetate and triethanolamine solution were added to carbopol solution and the pH was then adjusted to 7.4 by stirring the solution for 10 min. Then propylene glycol solution was added with stirring for 10 min until a clear consistent gel base was obtained.

Preparation of Gel Formulation

Three topical gel formulation was prepared using Terminalia Arjuna extract (petroleum ether extract of Terminalia Arjuna) and Annona squamosal extract (methanol bark extract of Annona squamosal) as per drug formulation manual where formulations were made using the gel base of carbopol 934 (0.75 g). Details of formulation compositions are recorded in Table 1.

Table 1: Formulation table.

Gel code	Terminalia Arjuna extract (ml)	Annona squamosal extract (g)	Carbopol 934 (g)	Triethanol amine (g)	Disodium EDTA (g)	Propylene Glycol (g)	D.M. water (50 g)
F1	1ml	0.5ml	1.5 g	1.5 g	0.005 g	5 g	q.s
F2	1ml	1ml	1.5 g	1.5 g	0.005 g	5 g	q.s
F3	0.5ml	1ml	1.5 g	1.5 g	0.005 g	5 g	q.s

Evaluation Parameters

Extrudability

About 20 g of gel were tightly packed into a closed, collapsible tube, which was secured at the crimped end with a clamp to stop it from rolling back. The gel was extruded after the cap was taken off. Weighing and collecting the extruded gel's quantity was done. It was determined what percentage of the extruded gel.

pH Measurement

pH measurement of the gel was carried out using a digital pH meter by dipping the glass electrode completely into the gel system to cover the electrode (**Figure 1**). The measurement was carried out in triplicate and the average of the three readings was recorded using a digital pH meter, the gel's pH was measured by fully submerging the glass electrode in the gel system to cover the electrode. Three readings were taken during the measurement, and the average of the three was noted.

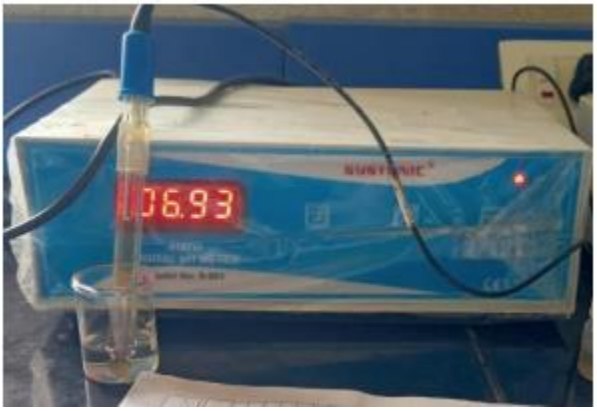

Figure 1: Determination of pH.

Moisture content

Moisture content and loss on drying (LOD) are significant characteristics for plant-based goods. Inadequate drying of these agents may result in the enzymatic breakdown of active ingredients. The LOD technique was used to determine the moisture content of the preparation. 5 gm of sample was carefully weighed and placed in a previously weighed petri plate (W1). W2 is the weight of the petri dish containing the sample. The petri dish was heated in a hot air oven at 100-108°C until the sample's contestant weight was reached. Measured the weight after 1 hour up to standard weight.

Rheological Evaluation

It included evaluating powder properties. The sample was evaluated using several physical requirements such as angle of repose, bulk density, tapped density, and Hausner's ratio.

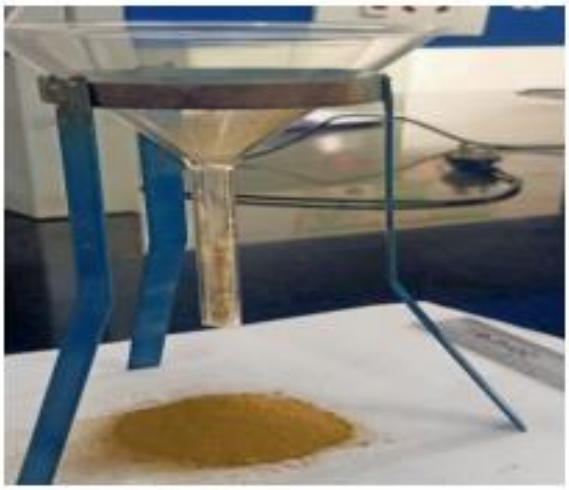

Figure 2: Measuring angle of repose.

Angle of Repose

The height and radius of the heap are noticed and recorded after the requisite amount of dried powder is dropped from a height of 6 cm (**Figure 2**). The angle of repose (θ) for the above approach can be calculated the using the formula:

$$\text{Angle of repose } (\theta) = \tan H \backslash R$$

Where, θ - Angle of repose

H - Height of the heap,

R - Radius of the base

Bulk Density: It is the amount of a substance in a certain volume. It is determined by dividing the given mass of powder by its bulk volume. It is calculated by using a funnel to transfer an accurately weighed amount of powder sample to the graduated cylinder.

The initial volume was recorded. The weight-to-volume ratio was computed using a formula:

$$\text{Bulk density} = \text{Mass of powder} \backslash \text{Volume of powder}$$

Tapped Density

It is calculated by placing a known amount of powder (10 gm) into a graduated cylinder and tapping it a certain number of times. The starting volume was reported. For 10-15 minutes, the graded cylinder was tapped continually. The density can be calculated by dividing the mass of the powder by the tapped volume.

$$\text{Tapped density} = \text{Mass of powder} \backslash \text{Tapped volume}$$

Housner's ratio

The Hausner's ratio can be used to determine the flowability of powders. It is the ratio of the powder's tapped density to its bulk density.

$$\text{Housner's ratio} = \text{Tapped Density} \backslash \text{Bulk Density}$$

Carr's index

The powder flow property, often known as percent compressibility, is also measured. It is proportional to the relative flow rate of cohesiveness and particle size. To get the % compressibility index, use the following equation:

$$\text{Carr's index} = \frac{\text{Tapped density} - \text{Bulk density}}{}$$

Tapped density × 100

Particle size

Particle size was performed by microscopic method as per standard procedure. Particle size analysis is an important parameter, which directly affects various properties of powder namely spreadability, grittiness, etc.

Washability

Formulation was applied on the skin and then ease and extent of washing with normal tap water were checked manually.

Appearance and Homogeneity

Visual perception was used to assess the prepared gels' physical appearance and uniformity. Physical appearance evaluations were done on things like colour, smell, appearance, texture, and smoothness. For the evaluation of colour and texture, touch sensation and visual perception were used, respectively.

Viscosity

The viscosity was measured Using a Brookfield viscometer (S-62, model LVDV-E) at 25 °C and a spindle speed of 12 rpm, [11].

Spreadability

Standard-sized glass slides were taken in two sets. One of the slides had the herbal gel formulation applied to it. The gel was sandwiched between the two slides in an area that was occupied by a distance of 7.5 cm along the slides when the other slide was placed on top of the gel. Gel weighing one hundred grams was applied on the upper slides, and the gel between the two slides was evenly compressed to create a thin layer. After removing the weight, the extra gel that was sticking to the slides was scraped off. The two slides in place were securely fastened to a platform so that only the upper slides could come off by themselves when weight was applied to them. Carefully, a 20 g weight was fastened to the upper slide. It was recorded how long it took the higher slide, acting as a force of gravity, to move 7.5 cm and separate from the bottom slide. Three iterations of the experiment were conducted, and the mean time was calculated [12].

Spreadability was calculated by using the following formula:

$$S = m \times l/t$$

Where, S= spreadability,

m-weight tied to upper slides (20 g),

l- Length of the glass slide (7.5 cm),

t- Time taken in sec.

Test for Irritancy

The prepared herbal gel for the treatment of pain and inflammation was applied to a previously marked region of 1 square cm on the left-hand dorsal surface, and time was recorded. The skin was then examined at regular intervals for irritancy, erythema, and oedema (if any) for up to 24 hours [13].

Stability studies

The main objective of the stability testing is to provide evidence on how the quality of the drug product varies with time under the influence of temperature and humidity. The stability study for the topical herbal gel formulation was done as per ICH guidelines in a stability chamber for a period of 3 months. A humidity chamber (floor standing model, three units in one with individual humidity and temperature controller, 300 X 300 X 300 mm, 15–60°C, Technico, India) was loaded with the chosen topical herbal gel formulation, which contained 2% of each CHME and VNME. The temperature ranges were 25°C ± 2°C/60% RH ± 5% RH, 32°C ± 2°C/60% RH ± 5% RH, and 40°C ± 2°C/75% RH ± 5% RH. At the beginning, first, second- and third-month samples were removed, and their color, odor, homogeneity, pH, viscosity, net content, microbial load, and sterility test results were assessed.

Result and Discussion

In general, gel formulation is more preferred, among the other topical semisolid preparations, since it has long residence time on the skin, high viscosity, moisturizing effect on flaky skin due to their occlusive properties, more bio adhesiveness, less irritation, independent of water solubility of active ingredient, ease of application and better release characters. Many studies have indicated that flavonoids such as luteolin and apigenin in herbs possess anti-inflammatory and antianalegics activity. Further, these polyphenolic flavonoids, apigenin and luteolin reported that they can penetrate the human skin and hence a topical herbal

gel formulation was designed containing these flavonoids for the treatment of pain and inflammation.

Appearance and Homogeneity

The current study's herbal face pack was tested for several organoleptic factors, and its observations such as colour, odour, texture, and smoothness are shown in Table 2.

Table 2: Appearance and Homogeneity

S.N.	Parameters	Observations		
		F1	F2	F3
1	Appearance	translucent	translucent	Translucent
2	Color	greenish	Greenish	Dark greenish
3	Odor	pleasant	Pleasant	Pleasant
4	Texture	homogenous	homogenous	Homogenous
5	Smoothness	smooth	Smooth	Smooth

Rheological Evaluation

The observations of rheological evaluation such as bulk density, tapped density, Angle of repose, Housner's ratio, Carr's index, are given in table 3. This supports the face pack's flow qualities, as it was discovered to be a free flowing and non-sticky powder in nature.

Table 3: Result of Rheological properties

S.N	Parameters	Observation			Inference
		F1	F2	F3	
1	Bulk density	0.40	0.41	0.44	Good
2	Tapped density	0.63	0.56	0.58	Good
3	Housner's ratio	1.34	1.40	1.44	Passable
4	Carr's ratio	22.6%	23.5%	24.4%	Passable
5	Angle of repose	32.4	33	35	Between 31-35° is considered as Good

Extrudability

About 20 g of gel were tightly packed into a closed, collapsible tube, which was secured at the crimped end with a clamp to stop it from rolling back. The gel was extruded after the cap was taken off. Weighing and collecting the extruded gel's quantity was done. It was determined what percentage of the extruded gel is 10% (**Table 4**).

Table 4: Result of extrudability.

S. No	Parameter	Observation		
		F1	F2	F3
1	Extrudability	4.5%	10%	11.1%

Physicochemical Parameters

Physicochemical parameters such as pH and Moisture content. The pH of the herbal gel treatment of pain and inflammation is determined to be close to that of the skin, and swelling index is examined in the second technique. As a result, the formulation can be regarded skin-safe (**Table 5**).

Table 5: Result of Physicochemical Evaluation.

S.N.	Parameters	Observations		
		F1	F2	F3
1	pH	7.91	5.85	7.56
2	Moisture Content	1.906	1.312	1.902

Spreadability

Standard-sized glass slides were taken in two sets. One of the slides had the herbal gel formulation applied to it. The gel was sandwiched between the two slides in an area that was occupied by a distance of 7.5 cm along the slides when the other slide was placed on top of the gel. Gel weighing one hundred grams was applied on the upper slides, and the gel between the two slides was evenly compressed to create a thin layer. After removing the weight, the extra gel that was sticking to the slides was scraped off. The two slides in place were securely fastened to a platform so that only the upper slides could come off by themselves when weight was applied to them. Carefully, a 20 g weight was fastened to the upper slide. It was recorded how long it took the higher slide, acting as a force of gravity, to move 7.5 cm and separate from the bottom slide. Three iterations of the experiment were conducted, and the mean time was calculated (**Table 6**).

Table 6: Result of spreadability test

Formulation	Weight (g)	Slide to travel the distance (cm)	Time (s)	Spreadability (g.cm/sec)
F1	20 g	7.5 cm	200 S	0.75 g.cm/sec
F2	20 g	7.5 cm	120 S	1.25 g.cm/sec
F3	20 g	7.5 cm	90 S	1.66 g.cm/sec

Irritancy test

When the formulation was put to the irritancy test, it showed no symptoms of rashes, redness, irritation, or swelling throughout the test (**Table 7**).

Table 7: Result of Irritancy test

S.N.	Parameters	Observations			
		F1	F2	F3	
1	Irritancy	Negative	Negative	Negative	No sign of erythema, oedema and irritation was observed
2	Erythema	Negative	Negative	Negative	
3	Oedema	Negative	Negative	Negative	

Washability

The face pack can be simply removed from the skin with tap water.

Tabe 8: Result of Washability test

S. N	Parameters	Observation		
		F1	F2	F3
1	Washability	Easily washable	Easily washable	Easily washable

Stability

In order to ensure the quality, safety and efficacy throughout the shelf life, stability study was performed as per ICH guidelines for F2 formulation (prepared using carbopol 934) as it exhibited better quality characteristics. No change in color, odour, homogeneity, pH, viscosity and net content of the topical herbal gel formulation was observed for this formulation after 0,1,2 and 3 months of stability testing.

Method for application

Take the prepared herbal gel in a bowl and apply it generously to the affected area. Allow the gel to absorb into the skin for 10-15 minutes. Once absorbed, gently massage the area and then wipe off any excess gel with a clean cloth before rinsing the area with water.

Conclusion

The study successfully formulated and evaluated a novel multi-herbal gel designed for the management of pain and inflammation. The optimized formulation demonstrated desirable physicochemical properties, including stability, spreadability, and viscosity, which are essential for effective topical application. In vitro and in vivo evaluations revealed that the gel exhibited significant anti-inflammatory and analgesic activities, comparable to standard treatments. The synergistic effect of the selected herbal components contributed to the observed therapeutic efficacy, underscoring their potential as a natural alternative to synthetic drugs with minimal side effects.

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Conflict of Interest

None declared.

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