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Enhanced Anti-Inflammatory Activity of *Passiflora edulis* Leaf Extract Nanoparticle Gel in Carrageenan-Induced Rat Model

Ni Made Dwi Sandhiutami, Yesi Desmiaty, Fahleni Fahleni, Rizqya Cahya Handayani, Windy Ciang

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Abstract: Passion fruit (*Passiflora edulis*) leaf extract is rich in flavonoids, which possess anti-inflammatory properties. This study aimed to enhance the anti-inflammatory effect of the extract through a nanoparticle gel formulation. Nanoparticles of the extract (NEP) were prepared using ionic gelation with a Carbomer 940 base. The anti-inflammatory efficacy of NEP was evaluated *in vivo* using a carrageenan-induced paw edema model in rats. Five groups (n=5) were tested: a negative control (Carbomer 940 gel base), a positive control (Sodium Diclofenac), and three NEP formulations with concentrations of 1% (NEP-1), 3% (NEP-2), and 5% (NEP-3). The NEP gels were homogeneous with a faint yellow color and a characteristic odor. Their spreadability ranged from 7.50 ± 0.67 cm to 7.69 ± 1.26 cm, viscosity exhibited plastic flow properties, and pH values were within 4.47 ± 0.06 to 5.20 ± 0.10. The anti-inflammatory effectiveness of NEP formulations increased with concentration, achieving edema inhibition rates of 3.66% (NEP-1), 68.47% (NEP-2), and 82.37% (NEP-3). In conclusion, the nanoparticle gel formulations of passion fruit leaf extract demonstrated good physical properties, with NEP-3 being the most effective in reducing carrageenan-induced paw edema in rats.

Introduction

When tissue is damaged, the body's natural response is an inflammatory reaction to repair the affected area (1). This response is characterized by swelling (edema), redness, heat, pain, and structural or functional changes, all indicating an increased immune reaction necessary for wound healing (2, 3). Anti-inflammatory drugs are commonly used to alleviate these symptoms. These drugs fall into two main categories: steroidal anti-inflammatory drugs (SAIDs) and nonsteroidal anti-inflammatory drugs (NSAIDs) (4, 5). While both classes inhibit inflammatory markers through different mechanisms, their use is associated with serious side effects, including peptic ulcers, renal hypertension, and bleeding, particularly in elderly individuals and patients with heart disease (6). The risks are heightened with prolonged use and high dosages. As a result, there is growing interest in herbal medicines derived from plants to minimize these adverse effects.

Recent studies suggest that plant-based treatments offer a promising alternative with comparable efficacy and fewer side effects. One such plant is *Passiflora edulis* var. flavicarpa Degener, commonly known as passion fruit. Research has shown that its leaf extract possesses anti-inflammatory properties due to its flavonoid, alkaloid, and steroid/triterpenoid content (7, 8). Additionally, this plant has been traditionally used to treat conditions such as constipation, dysmenorrhea, dysentery, and insomnia (9). Despite these benefits, oral administration of herbal medicine faces challenges, including drug degradation before reaching the target site, limiting its effectiveness in treating inflammation.

To address these limitations, topical drug delivery has gained attention due to its localized action, which directly inhibits cyclooxygenase (COX) activity involved in inflammation (10, 11). Unlike oral medications, topical formulations reduce systemic side effects while improving drug targeting and efficacy. Nanoparticle-

based drug delivery systems have emerged as a promising strategy to further enhance the therapeutic potential of herbal medicines. Nanoparticles improve drug stability, bioavailability, and absorption while minimizing unintended interactions within the body (12). By reducing the required dosage, nanoparticle formulations also mitigate potential side effects (13).

This study explores the formulation of a nanosized passion fruit leaf extract (NEP) gel to enhance its anti-inflammatory effect as a novel herbal medicine. Gels are particularly suitable for topical application due to their ease of use, rapid absorption, and ability to provide a cooling sensation (14-17). The nanoscale size of the particles improves skin penetration, allowing for better therapeutic outcomes. Carbomer 940, a widely used gelling agent in cosmetic and pharmaceutical formulations (18), serves as the gel base in this study. The effectiveness of NEP gel was evaluated through *in vivo* anti-inflammatory tests using carrageenan-induced paw edema in male rats.

NEP gel formulations with concentrations of 1%, 3%, and 5% were tested, with sodium diclofenac as a positive control and an untreated group as a negative control. Inflammatory responses in the rats were monitored through visual indicators such as redness and swelling (19), which result from vascular changes that increase blood flow and edema formation. These inflammatory changes occur rapidly, often within seconds, lasting minutes to hours. By assessing the efficacy of NEP gel in reducing inflammation, this study aims to provide a safer and more effective alternative to conventional anti-inflammatory treatments.

Methodology or Experimental Section

Materials and Tools

Passion fruit leaf extract (*Passiflora edulis*) obtained from BALITRO, Bogor. Other materials used were chitosan (Chimultiguna), NaTPP (Arrow Fine Chemicals India), Carbomer 940 (Fagron), propylene glycol (Brataco), methyl paraben (MedChenExpress), aquadest (PT. Arbe Chemindo), carrageenan (IndoFoodChem), and diclofenac sodium gel (PT Novell). The tools used were analytical scales, glassware, and volumetric tools, microbalance MTS (Mettler, Australia), scanning electron microscopy MA 10 (Zeiss, UK), oven (Memmert, Germany), freeze dryer SB 6 (Chemlab, UK), silica gel plate F2s4, chamber (CAMAG, Switzerland), UV lamp cabinet (CAMAG, Switzerland), UV-Vis spectrophotometer 1800-UV (Shimadzu, Japan), pH meter HI 2211 (HANNA, Japan), densitometer (CAMAG, Switzerland), Brookfield viscometer, Mercury plethysmometer, particle size analyzer (Malvern, England) and Zeta sizer DelsaNanoTM (Beckman Coulter, USA).

NEP Gel Formulation

The hydrogel base was prepared by dissolving Carbomer 940 in distilled water, with the addition of Triethanolamine to facilitate gel formation due to the acidic nature of Carbomer 940. Methylparaben was added as a preservative to extend the shelf life of the topical preparation. Propylene glycol was used as a solvent for a more homogeneous gelling agent.

Nanoparticle extract of passion fruit leaves (NEP), which had been developed and characterized in previous studies (20), was incorporated into formulations at concentrations of 1%, 3%, and 5% to determine the optimal NEP gel composition. NEP gel was prepared using the ionic gelation method and was subsequently evaluated for its particle size, polydispersity index, gel quality, and anti-inflammatory effectiveness on the feet of male rats induced with carrageenan

In Vivo Experimental Design

Animal Preparation

In vivo testing was conducted after obtaining approval from the Ethics Committee, Faculty of Medicine, University of Indonesia (KET-396/UN2.F1/ETIK/PPM.00.02/2024). This test was conducted at the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Pancasila University, Indonesia. Twenty-five male white rats (*Rattus norvegicus*) of the Wistar strain were randomly divided into five groups (n=5). All experimental animals were acclimatized for approximately one week to adapt to the environment, control their health and body weight, and were given uniform nutritional food. Before the experiment, the rats were fasted for approximately 18 hours while still being given water so that the absorption of the test substance was not disturbed by food.

Anti-inflammatory Activity Test in Rats

The method for assessing the anti-inflammatory effects in rats induced with carrageenan utilized a plethysmometer to specifically measure the volume of edema or swelling in the feet of experimental animals during inflammation. Twenty-five rats were divided into five groups, each consisting of five rats with marks. Each group received different treatment. The positive control group was treated with sodium diclofenac gel, the negative control group received a gel base (Carbomer 940), the NEP-1 group received 1% NEP gel, the NEP-2 group received 3% NEP gel, and the NEP-3 group received 5% NEP gel. All NEP groups were treated with topical NEP gel 50 times, with dose adjusted to body weight. Markings were made on the ankle before immersing feet into the plethysmometer to measure edema volume. Thirty minutes after NEP gel administration, each foot sole was injected subplantarly with 1% carrageenan.

Table 1. NEP gel formulation characteristics.

Formula	50 RPM			100 RPM			150 RPM			Homogeneity
	Time (minutes)									
	10	15	20	10	15	20	10	15	20	
Base	+	+	+	+	++	++	+	++	+	Homogeneous
NEP-1	+	++	++	++	++	++	++	++	++	Homogeneous
NEP-2	+	++	+	++	++	++	++	++	++	Homogeneous
NEP-3	+	+	++	++	++	++	++	+++	+++	Homogeneous
Note: (+) indicates the gel's air bubble level.										

Data Analysis

Research data analysis was conducted using Area Under the Curve (AUC) calculations and the percentage of edema inhibition. AUC values for each treatment group were analyzed using the SPSS (Statistical Package for the Social Sciences) program. If the ANOVA test results indicated a statistically significant difference among treatments, the analysis was further conducted using the SRD (Smallest Real Difference) test at a significance level of 5% (α = 0.05) to determine whether there were differences between treatments.

The effectiveness of the NEP gel preparation as a topical anti-inflammatory agent was assessed by comparing its anti-inflammatory activity percentage to sodium diclofenac. The Area Under the Curve (AUC) was calculated using the **Equation 1**.

$$AUC = \frac{(V_{n-1} + V_n)(t_n - t_{n-1})}{2}$$ **Equation 1**

where, V_n is the volume of the rat's paw at the (n) hour/minute, and V_{n-1} is the volume of the rat's paw at the (n-1) hour/minute.

Results

The results of the NEP gel nanoparticle formulation demonstrated good gel characteristics. The characteristics of NEP gel nanoparticles were assessed by measuring particle size and the polydispersity index using a Particle Size Analyzer (Malvern). Previous research (20) reported a particle size of 187.6 nm.

Several studies have investigated nanoparticle-based gel formulations to enhance drug delivery systems. Prior research on NEP gel nanoparticles explored various formulation parameters to optimize particle size, stability, and bioavailability. The standard size range for nanoparticles is 1–1000 nm; therefore, the obtained particle size met these requirements, with a polydispersity index value of 0.626.

Table 1 presents the air bubbles formed during the stirring process at different speeds. The time required for air bubble dissipation during the resting phase indicates the gel's stability. The highest air bubbles were observed at a stirring speed of 150 rpm, particularly in NEP-3. Excessive air bubbles can indicate air entrapment rather than improved homogeneity. However, while 150 rpm produced the most bubbles, NEP-3 gel was still clear and dispersed well.

The data in **Table 2** show color and odor intensity variations depending on the extract concentration in the formula. A passion fruit aroma in the NEP gel indicates the successful incorporation of its aromatic components.

All formulations, including the base and NEP variants, exhibited a uniform semi-solid consistency. Among them, the NEP-3 formulation demonstrated the most balanced spreadability—not too runny or too thick—making it more effective in covering the diameter of inflammatory wounds. NEP-3 also had the highest viscosity, which can influence both application ease and absorption rate.

The pH of the NEP formulations ranged between 4.47 and 5.20, suggesting that they are within a skin-compatible range and unlikely to irritate.

Table 2. NEP gel formulation evaluation.

Formula	Shape	Color	Odor	Spread Power ± SD (cm)	pH ± SD	Viscosity (cPs)
Base	Semi-solid	Clear	no	6.14 ± 0.20	4.57 ± 0.1527	7663
NEP-1	Semi-solid	Slightly faded yellow	Passion Fruit	7.69 ± 1.26	4.93 ± 0.2309	4701
NEP-2	Semi-solid	Faded yellow	Passion Fruit	7.50 ± 0.67	5.20 ± 0.1	4243
NEP-3	Semi-solid	Faded yellow	Passion Fruit	7.51 ± 0.18	4.47 ±0.0577	6117

Table 3. Average volume of edema in rat paws.

Group	Average Volume of Rats Paw Edema at Hour						AUC ± SD	Anti-inflammatory Test	
	1	2	3	4	5	6		Inhibition	Effectiveness
Negative Control	1.0075	1.46	1.64	1.86	1.88	1.730	8.2087 ± 0.41	-	-
Positif Control	0.98	1.28	1.29	1.13	0.96	0.900	5.6100 ± 0.23	31.66%	-
NEP-1	0.98	1.59	1.60	1.93	1.62	1.770	8.1130 ± 0.45	1.16%	3.66%
NEP-2	1.23	1.18	1.46	1.39	1.39	1.340	6.4290 ± 0.46	21.68%	68.47%
NEP-3	1.00	1.16	1.22	1.31	1.36	1.035	6.0675 ± 0.35	26.08%	82.37%

In Vivo Test of NEP Gel

Carrageenan is a class of galactan polysaccharides (21) that can irritate and cause edema (18). It can release inflammatory mediators such as histamine and serotonin, which cause edema due to the presence of antibodies in test animals that react to antigens to counteract their effects (22).

Table 3 provides data for determining the percentage of inhibition and the anti-inflammatory effectiveness of NEP gel formulations. The edema volume in the positive control and NEP-2 groups peaked at the third hour, with NEP-2 showing a higher edema volume. In contrast, edema volume peaked at the fourth hour in the NEP-1 group and the fifth hour in the NEP-3 group.

The effectiveness of anti-inflammatory drugs was assessed by tracking changes in edema volume in the soles of the rats' feet and by calculating the Area Under the Curve (AUC). A higher AUC value indicates lower anti-inflammatory effectiveness.

As shown in **Table 3**, the positive control group (Sodium Diclofenac) exhibited the highest edema inhibition. NEP-3 (5% concentration) demonstrated the best inhibitory effect among the test formulations, reducing edema by 26.08%. While slightly lower than the positive control, NEP-3 retained 82.37% of the positive control's anti-inflammatory effectiveness.

Discussion

Passion fruit leaves contain important flavonols with proven health benefits, including anti-inflammatory properties. However, flavonoid compounds often exhibit low solubility in water, poor molecular stability, and limited bioavailability (23). This study aimed to formulate a Passion Fruit Leaf Nanoparticle Extract (NEP) in gel form to enhance its anti-inflammatory effects. The nanoherbal gel formulation was developed as an alternative to existing drugs to minimize side effects.

Previous research (20) reported that the nanoparticle extract had an optimal particle size of 187.6 nm, with a polydispersity index of 0.626 and a zeta potential of +31.2 mV. To identify the most effective formulation, three variations of nano extract concentrations—NEP-1, NEP-2, and NEP-3—were tested. The formulations were evaluated based on SNI standards, including organoleptic properties, homogeneity, spreadability, pH, and viscosity (24).

The evaluation results confirmed the success of the NEP gel formulation. The intensity of color and odor increased with higher extract concentrations. The base formulation was clear and odorless, whereas all NEP formulations exhibited a distinct passion fruit aroma. NEP-1 had a slightly faint yellow color, while NEP-2 and NEP-3 had a more noticeable yellow hue.

Homogeneity was assessed by analyzing air bubble formation. A higher number of air bubbles in the gel suspension indicated a more uniform distribution of particles within the gel matrix. The gel stirred at 150 rpm produced numerous air bubbles that dissipated quickly, suggesting that all components in the formula were evenly distributed without phase separation.

Spreadability reflects the gel's ability to distribute evenly over a surface, while viscosity is a key factor influencing its stability and ease of application. Both properties are crucial for ensuring a gel's consistency and user comfort. The base formulation exhibited the lowest spreadability (6.14 ± 0.20 cm) and the highest viscosity (7663 cPs), indicating a thicker consistency with reduced spreadability. However, all NEP formulations demonstrated increased spreadability compared to the base formulation, suggesting improved application properties and enhanced skin absorption.

Among the NEP variants, NEP-1 had the highest spreadability (7.69 ± 1.26 cm), NEP-2 had the lowest viscosity (4243 cPs), and NEP-3 exhibited both the highest viscosity (6117 cPs) and notable spreadability (7.51 ± 0.18 cm). These findings indicate that incorporating NEP reduces gel viscosity, as formulations with lower viscosities tend to spread more easily. This effect may be attributed to NEP's nature as a nanosuspension containing surfactant extracts (25), which can weaken the gel structure and lower its viscosity. Conversely, the increased viscosity in NEP-3 may result from interactions between the gel matrix and nanosuspension, possibly due to a higher

concentration of certain components that enhance molecular cohesion. Regarding flow properties, NEP-1 exhibited thixotropic behavior, meaning its viscosity decreased under shear stress, making it easier to apply. In contrast, NEP-2 and NEP-3 demonstrated anti-thixotropic behavior, requiring greater pressure to dispense the gel from the tube.

The anti-inflammatory effectiveness of NEP gel was evaluated *in vivo* using male rats as experimental models. The study tested three different concentrations of NEP gel: 1% (NEP-1), 3% (NEP-2), and 5% (NEP-3). Flavonoids, present in NEP, are believed to contribute to its anti-inflammatory activity (26, 27). The anti-inflammatory test followed the Winter Method, a widely used and quantitative approach for assessing inflammation by measuring changes in edema volume (mL) over time (hours). Carrageenan was used as the chemical inducer of inflammation due to its ability to stimulate phospholipase A2 and activate the complement system, leading to an inflammatory response (28). This method was chosen because it does not cause lasting tissue damage and provides a reliable comparison of anti-inflammatory drug effectiveness.

Visually, inflammation in the rat's foot was identified by redness and swelling caused by increased blood flow and fluid accumulation in the tissue. These inflammatory responses are triggered within seconds and can last several hours (18). The edema volume was measured using a plethysmometer connected to a burette, with mercury used as the displacement liquid due to its non-wetting properties. The measurement is based on Archimedes' principle, where the displaced volume corresponds to the swelling degree. Methylene blue was added to the burette to enhance measurement readability. To ensure accuracy, the left foot was always used to prevent interference from the rat's other foot during measurement.

Baseline (hour 0) measurements confirmed that no rats exhibited pre-existing edema before carrageenan induction. The observation period lasted six hours, as this was the timeframe in which peak edema formation and subsequent resolution occurred (29). Results showed that the negative control group exhibited minimal edema reduction, consistent with previous research (7, 30), as the gel base lacked active anti-inflammatory components. In contrast, the positive control and NEP formulations demonstrated significant edema inhibition. Statistical analysis revealed that edema reduction was significant in the positive control and NEP groups compared to the negative control. Edema inhibition was observed starting two hours after carrageenan induction, suggesting that both diclofenac sodium and NEP formulations effectively suppressed inflammatory mediator release, including prostaglandins (31).

Further statistical analysis showed significant differences between the positive control (diclofenac sodium) and the NEP groups (NEP-1, NEP-2, NEP-3). Diclofenac sodium exhibited superior anti-inflammatory activity compared to the NEP formulations. However, within the NEP groups, the 5% concentration (NEP-3) demonstrated the strongest anti-inflammatory effect, as indicated by its lower Area Under the Curve (AUC) value. The AUC analysis showed that a lower AUC corresponds to greater anti-inflammatory effectiveness. NEP-3 achieved an AUC value of 6.0675 ± 0.35, proving it to be the most effective among the NEP formulations. While diclofenac sodium was more effective overall, NEP-3 showed a comparable level of anti-inflammatory activity with fewer potential side effects, making it a promising alternative for anti-inflammatory treatment.

The results of the anti-inflammatory test on the nanoparticle gel extract of passion fruit leaves (NEP) at concentrations of 1%, 3%, and 5% demonstrated its effectiveness in reducing inflammation. The edema inhibition percentages for NEP-1, NEP-2, and NEP-3 were 1.16%, 21.68%, and 26.08%, respectively. Additionally, the effectiveness of NEP gel, when compared to the positive control, was 3.66%, 68.47%, and 82.37% for each concentration.

The pH value of the NEP formulations ranged between 4.47 and 5.20, confirming that the gel is safe for topical application without causing skin irritation in rats. The anti-inflammatory action of NEP gel is attributed to its flavonoid content, which inhibits the cyclooxygenase (COX) enzyme, thereby reducing the production of arachidonic acid and suppressing the release of histamine. This mechanism contributes to the gel's anti-inflammatory properties (32, 33).

Based on these findings, NEP-3 (5% concentration) exhibited the highest anti-inflammatory activity, effectively reducing edema formation in rats. These results suggest that NEP-3 is the most promising formulation for potential therapeutic applications.

Conclusion

The nanosized passion fruit leaf extract (NEP) gel, formulated using Carbomer 940, meets the requirements for high-quality gel preparation. The anti-inflammatory effectiveness of NEP-1, NEP-2, and NEP-3 was 3.66%, 68.47%, and 82.37%, respectively, demonstrating significant edema inhibition in male white rats induced by carrageenan. NEP-3 (5% concentration) among the formulations exhibited the highest anti-inflammatory activity, making it the most effective in reducing edema.

Further research is recommended to investigate the chemical markers of inflammation in NEP gel

formulations to better understand its mechanism of action and potential therapeutic applications.

Abbreviations

NEP = Nanoparticle extract of passion fruit leaves; AUC = Area Under Curve; SAIDs = Steroidal Anti-Inflammatory Drugs; NSAIDs = Nonsteroidal Anti-Inflammatory Drugs; SPSS = Statistical Package for the Social Science; SRD = Smallest Real Difference.

Declarations

Author Informations

Ni Made Dwi Sandhiutami
Affiliation: Pancasila University Faculty of Pharmacy.
Contribution: Conceptualization, Methodology, Supervision, Writing - Review & Editing.

Yesi Desmiaty
Affiliation: Pancasila University Faculty of Pharmacy.
Contribution: Resources, Software, Writing - Review & Editing.

Fahleni Fahleni
Affiliation: Pancasila University Faculty of Pharmacy.
Contribution: Resources, Writing - Review & Editing.

Rizqya Cahya Handayani
Affiliation: Pancasila University Faculty of Pharmacy.
Contribution: Data Curation, Formal analysis, Project administration, Validation, Writing - Review & Editing.

Windy Ciang ✉
Affiliation: Pancasila University Faculty of Pharmacy.
Contribution: Data Curation, Formal analysis, Investigation, Project administration, Writing - Original Draft, Writing - Review & Editing.

Conflict of Interest

The authors declare no conflicting interest.

Data Availability

The unpublished data is available upon request to the corresponding author.

Ethics Statement

In vivo testing was conducted after obtaining approval from the Ethics Committee, Faculty of Medicine, University of Indonesia (KET-396/UN2.F1/ETIK/PPM.00.02/2024).

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