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ORIGINAL ARTICLE

Development of a Sprayable Thermosensitive Hydrogel Containing Rambutan (*Nephelium Lappaceum* L) Leaf Extract for Diabetic Wound Therapy

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Abstract

Background/Aim: Diabetic wounds are challenging to treat due to impaired healing processes. This study aimed to develop a sprayable thermosensitive hydrogel incorporating rambutan (*Nephelium lappaceum* L) leaf extract, known for its phytochemical wound healing potential.
Methods: Rambutan leaves were extracted via 70 % ethanol maceration. Qualitative and quantitative analyses confirmed the presence of tannins and flavonoids. The extract was formulated into thermosensitive hydrogels (F1–F3) using sodium alginate, Poloxamer 407 and Poloxamer 188. Physical properties were evaluated and wound healing efficacy was tested on diabetic rats over 21 days using a full-thickness wound model.
Results: The extract yielded 25.44 % with tannin and flavonoid contents of 2.94 % and 5.73 %, respectively. All formulations were homogeneous, pH-balanced (4.52–5.03) and met ideal criteria for spreadability, gelation, swelling and viscosity. *In vivo* tests showed F3 had the highest wound healing rate (81.25 %), approaching the normal control (84.00 %) and outperforming the reference drug (61.67 %). Statistical analysis indicated significant differences ($p < 0.05$).
Conclusion: The thermosensitive hydrogel with rambutan leaf extract effectively accelerates diabetic wound healing and shows potential as a topical therapy.

Key words: *Sapindaceae*; *Nephelium lappaceum*; Plant leaves, extract; Hydrogels, thermosensitive; Diabetes mellitus; Diabetic foot; Wound injuries; Wound healing.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterised by persistent hyperglycaemia due to impaired insulin secretion, action, or both.[1, 2] Globally, the prevalence of DM continues to rise, posing a serious public health concern. According to the World Health Organisation (WHO), more than 422 million people worldwide were estimated to be living with diabetes by 2020.[3] One of the most challenging complications of diabetes is the development of diabetic wounds, particularly diabetic foot ulcers, which are notoriously difficult to heal and are associated with prolonged recovery periods, frequent infections and a high risk of amputation.[4, 5]

The impaired wound healing in diabetic patients results from a complex interplay of factors, including reduced angiogenesis, neuropathy, compromised immune responses and chronic inflammation.[6] Clinically, the management of diabetic wounds often involves the administration of systemic or topical antibiotics to control infection.[7] However, inappropriate or prolonged use of antibiotics has been associated with treatment failure, microbial resistance, delayed tissue regeneration and increased healthcare costs.[8] As such, diabetic wound care requires a comprehensive and individualised approach that incorporates wound debridement, pressure offloading and rigorous infection control measures tailored to the wound's severity and the patient's condition.[7, 9]

Given the limitations of conventional therapies, there is an increasing interest in alternative and adjunctive treatments derived from natural sources. Medicinal plants have long been utilised in traditional medicine and are gaining scientific recognition for their therapeutic potential in modern wound care.[10] One such promising candidate is the rambutan plant (*Nephelium lappaceum* L), particularly its mature dark green leaves, which have demonstrated wound healing activity in several preclinical studies.[11] The leaves are rich in bioactive compounds, including tannins, flavonoids, alkaloids and saponins. Tannins exhibit antimicrobial and astringent properties that aid in tissue contraction and wound closure, while flavonoids contribute to anti-inflammatory effects by modulating pro-inflammatory cytokines and oxidative stress.[12, 13] Tannins work by binding to proteins in microbial cell walls, disrupting their function and leading to the inhibition of microbial growth, while also promoting tissue contraction to aid wound healing.[12] Flavonoids modulate the immune response by decreasing the production of pro-inflammatory cytokines and scavenging free radicals, which reduces oxidative stress and inflammation.[13] Additionally, the antimicrobial and haemostatic activities of alkaloids by interfering with microbial DNA and enzyme functions, exhibiting antimicrobial effects and also aiding in blood clotting to control bleeding and saponins support their role in accelerating wound healing by enhancing the immune response and increasing the permeability of cell membranes, which helps eliminate pathogens and reduce inflammation.[14, 15]

While the pharmacological benefits of rambutan leaf extract are promising, the effectiveness of herbal-based therapies also depends significantly on the mode of delivery.[10] Recent advancements in pharmaceutical formulation have led to the development of sprayable thermosensitive hydrogels, which offer a novel, non-invasive and patient-friendly drug delivery system for topical applications.[16] These hydrogels are temperature-responsive they remain in a liquid state at room temperature and undergo gelation upon contact with body temperature, forming a protective gel layer over the wound without requiring direct contact.[17] This mechanism not only enhances targeted delivery and adherence to irregular wound surfaces, but also improves patient comfort and compliance.

The formulation of thermosensitive hydrogels typically involves biocompatible polymers such as sodium alginate, poloxamer 407 and poloxamer 188. Sodium alginate, a natural polysaccharide, supports cell proliferation and tissue regeneration while also exerting antibacterial effects.[18] Poloxamer 407 is widely used for its thermo-responsive properties and its ability to stimulate fibroblast proliferation, which plays a critical role in dermal repair.[17] Poloxamer 188 acts as a co-solubiliser and gelation temperature modulator, ensuring optimal viscosity and gel formation at physiological temperatures.[19] The synergistic combination of these excipients results in a hydrogel system that adapts to wound morphology, protects against microbial invasion and creates a moist healing environment.[20]

In light of the above, this study aimed to develop and optimise a sprayable thermosensitive hydrogel formulation incorporating rambutan leaf extract (*Nephelium lappaceum* L) as a natural therapeutic agent for diabetic wound care. The research focuses on evaluating the physicochemical characteristics, pharmaceutical performance and *in vivo* wound healing efficacy of the formulated hydrogel. It is anticipated that this innovative formulation will offer a safe, effective and accessible alternative to conventional wound treatments, especially for diabetic patients with chronic non-healing wounds.

Methods

This study was conducted from June to November 2023 at the Analytical Chemistry Laboratory and the Pharmaceutical Technology Laboratory,

Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia. During the extraction and preparation phase, tools such as a blender, standard laboratory glassware, muslin cloth, rotary evaporator, refrigerator, magnetic stirrer and water bath were utilised to process plant materials and prepare the extracts. For characterisation and measurement, instruments including a viscometer, pH meter, analytical balance, volumetric pipettes, micropipette tips and haematocrit pipettes were employed to analyse the physical and chemical properties of the samples. Biological testing involved the use of syringes, electric shaver, scalpel and glucose test strips. Throughout the study, materials such as gauze, cotton, tissue and sodium alginate were used as supporting components. The materials utilised in this research included gauze, cotton, tissue, sodium alginate, Poloxamer 407 (Sigma®, Darmstadt, Germany), Poloxamer 188 (Sigma®, Darmstadt, Germany), 96 % and 70 % ethanol, glycerol, rambutan leaf extract, distilled water, magnesium powder, hydrochloric acid, ferric chloride, streptozotocin, normal saline, male Wistar rats, standard rat chow, lidocaine and sodium citrate buffer with pH 4.0.

Preparation of extract and chemical analysis

The rambutan leaves (*Nephelium lappaceum* L) used in this study were collected from the Special Region of Yogyakarta Indonesia. Botanical identification was conducted at the Biology Laboratory of Ahmad Dahlan University to confirm the authenticity of the plant species. Extraction of rambutan leaves was performed using the maceration method.[21] Two hundred grams of dried powdered leaves were soaked in 500 mL of 70 % ethanol for 24 hours with occasional stirring. The resulting mixture was filtered using muslin cloth and further clarified through a Büchner funnel. The filtrate was concentrated using a rotary evaporator, followed by water bath evaporation to obtain a thick extract.[21]

Phytochemical screening was conducted to determine the presence of flavonoids and tannins, both qualitatively use tube test method, involved adding a few drops of 1 % $FeCl_3$ solution to the extract, where a dark green or blue colour showed the presence of tannins.[15] For flavonoids, the extract was combined with magnesium powder and concentrated hydrochloric acid and a yellow or red colour indicated a positive result.[15] Quantitative measurements of these compounds were then carried out using UV-Visible spectrophotometry.[22]

Formulation of sprayable thermosensitive hydrogel

To prepare the sprayable thermosensitive hydrogel, the base formulation was first developed. Sodium benzoate was dissolved in distilled water and stirred at 27 °C and 300 rpm, followed by the gradual addition of sodium alginate with continuous stirring using a magnetic stirrer. Subsequently, Poloxamer 188 and Poloxamer 407 were added slowly to ensure homogeneity.[18] Meanwhile, the thick rambutan leaf extract was dissolved in a small volume of distilled water using a mortar and pestle until fully dispersed. The extract solution was then incorporated into the base hydrogel formulation and homogenised thoroughly using a magnetic stirrer at constant speed to ensure even distribution of the extract throughout the formulation. The resulting formulations were subjected to physicochemical evaluations, including organoleptic examination such as appearance, colour, odour and consistency, pH measurement using a pH meter, assessing spreadability by placing a fixed amount of gel between glass plates, determining gelation time with a stopwatch, calculating swelling index by weighing samples before and after immersion in distilled water, measuring spray weight per actuation, checking viscosity with a viscometer and examining homogeneity visually for uniform texture and colour.

Animal model preparation

To evaluate the wound healing efficacy of the sprayable thermosensitive hydrogel containing rambutan (*Nephelium lappaceum* L) leaf extract, a diabetic wound model was developed using male Wistar rats. The induction of diabetes was carried out through a single intraperitoneal injection of streptozotocin (STZ) at a dosage of 40 mg/kg of body weight. The STZ solution was freshly prepared prior to administration by dissolving it in 0.1 M sodium citrate buffer at pH 4.0 to ensure chemical stability and effectiveness. Following induction, blood glucose levels were monitored after 24 to 48 hours using commercial glucose test strips via tail vein sampling. Rats exhibiting fasting blood glucose concentrations exceeding 200 mg/dL were classified as diabetic and selected for further experimentation.[23]

A total of twenty-four diabetic male Wistar rats,

each weighing between 180 and 250 grams, were randomly assigned into six experimental groups (n = 4 per group) to ensure balanced comparison. Group I served as the normal control, consisting of healthy rats that did not receive STZ but were treated with the reference standard drug for wound healing. Group II represented the diabetic control, consisting of diabetic rats treated with a standard reference drug commonly used for wound healing. Group III included diabetic rats treated with a placebo, which was the sprayable thermosensitive hydrogel formulation without the active extract. Groups IV, V and VI received sprayable thermosensitive hydrogel formulations containing 3 %, 5 % and 7 % rambutan leaf extract, respectively.

Before wound induction, all animals were anesthetised intramuscularly using 2 % lidocaine at a dose of 7 mg/kg body weight. The dorsal surface of each rat was shaved using an electric clipper and disinfected with 70 % ethanol to prevent contamination.[24] A full-thickness excisional wound approximately 1 cm^2 in diameter was created on the dorsum using a sterile biopsy punch under aseptic conditions. Wound healing progress was assessed on days 7, 14 and 21 post-treatment. Evaluations included wound diameter reduction, exudate presence, scab formation and emergence of granulation or new epithelial tissue, particularly indicated by spontaneous scab detachment. The percentage of wound healing (PL) was calculated using the following formula:

$$PL = \frac{\text{Initial wound diameter-Observation wound diameter}}{\text{Initial wound healing}} \times 100\ \%$$

Data analysis

The data collected were statistically analysed using one-way analysis of variance (ANOVA), followed by post hoc comparisons using the least significant difference (LSD) test. Statistical significance was determined at a confidence level of $p < 0.05$. Data analysis was performed using SPSS software version 22.0.

Results

Preparation of extract and chemical analysis

Rambutan leaf extract from a total of 800 grams of dried rambutan leaf powder was subjected to maceration using 70 % ethanol for 24 hours. Following solvent evaporation and concentration, the extraction process yielded 203.54 grams of thick extract, corresponding to a yield of 25.44 %. Qualitative analysis confirmed the presence of tannins and flavonoids. The addition of $FeCl_3$ reagent produced a dark blue colour, indicating tannins, while the addition of NaOH resulted in a reddish-yellow colour, indicating flavonoids.

Quantitative determination of tannin content was conducted using tannic acid as a standard. Based on the calibration curve $y = 27.583x + 0.0832$; $R^2 = 0.9836$, the extract showed absorbance values of 0.215, 0.228 and 0.293, resulting in an average tannin content of 2.94 % (w/v) in a 0.2 mg/mL solution. For flavonoid content, quercetin was used as the reference compound. The standard curve equation was $y = 9.05x - 0.1535$ ($R^2 = 0.9983$). Absorbance values of the extract samples were 0.339, 0.377 and 0.378, corresponding to an average flavonoid content of 5.73 % (w/v) in a 1 mg/mL solution.

Formulation of sprayable thermosensitive hydrogel

The sprayable thermosensitive hydrogel was formulated using sodium alginate, Poloxamer 407, Poloxamer 188, glycerine and sodium benzoate, with rambutan leaf extract as the active component. The base was prepared by sequentially dissolving the ingredients in distilled water with continuous stirring. The extract was dispersed separately, then added slowly into the base under magnetic stirring. To minimise oxidation, aluminium foil was used to shield the beaker during incorporation. All formulations resulted in stable, lump-free dispersions.

The physical evaluations included organoleptic observations, pH measurements, spreadability, gelation time, swelling index, spraying weight, viscosity and homogeneity. All formulas (F1, F2, F3) produced homogeneous, clear, brownish-yellow liquids with a characteristic herbal odour. The physical evaluation results are summarised in Table 1 and Table 2.

Animal model preparation

The percentage of wound healing was evaluated in diabetic rats for 21 days including a normal control (K1), diabetic control (K2), a placebo control (K3) and three test formulations (F1–F3). The wound closure percentages are presented in

Table 1: Physical evaluation results

Evaluation	Placebo	F1	F2	F3
pH	7.01 ± 0.02	5.03 ± 0.02	4.67 ± 0.03	4.52 ± 0.02
Spreadability (cm)	10.17 ± 0.15	5.20 ± 0.20	6.17 ± 0.15	6.68 ± 0.16
Gelation time (s)	52.33 ± 2.52	88.67 ± 4.58	85.00 ± 4.58	70.67 ± 6.03
Swelling index (%)	230.05 ± 83.27	201.29 ± 83.27	205.43 ± 83.01	206.86 ± 83.58
Spraying weight (g)	–	0.12 ± 0.02	0.10 ± 0.04	0.13 ± 0.04
Viscosity (cP)	808.92 ± 18.96	995.07 ± 3.47	933.71 ± 20.12	892.70 ± 21.29

F1, F2, F3: sprayable thermosensitive hydrogel formulations containing 3 %, 5 % and 7 % rambutan leaf extract, respectively;

Table 2: Organoleptic and homogeneity results

Formula	Organoleptic description	Homogeneity
Placebo	Liquid, clear, odourless	Homogeneous
F1	Clear brownish-yellow liquid, mild herbal scent	Homogeneous
F2	Slightly more concentrated brownish-yellow liquid, herbal scent	Homogeneous
F3	Most concentrated brownish-yellow liquid, strong herbal scent	Homogeneous

F1, F2, F3: sprayable thermosensitive hydrogel formulations containing 3 %, 5 % and 7 % rambutan leaf extract, respectively;

Table 3: Wound healing percentage after 21 days

Group	Description	Mean ± SD (%)	p-value vs K1	p-value vs K2	p-value vs K3
K1	Normal control	84.00 ± 6.20	—	0.632	0.015*
K2	Diabetic control	82.00 ± 6.36	0.632	—	0.022*
K3	Placebo control	61.67 ± 11.30	0.015*	0.022*	—
F1	Test formulation 1	77.92 ± 10.10	0.214	0.192	0.191
F2	Test formulation 2	75.83 ± 5.16	0.114	0.134	0.134
F3	Test formulation 3	81.25 ± 7.76	0.548	0.462	0.027*

**Significant; One-way ANOVA indicated significant differences among groups (p = 0.010); F1, F2, F3: sprayable thermosensitive hydrogel formulations containing 3 %, 5 % and 7 % rambutan leaf extract, respectively;*

Table 3. Statistical analysis using one-way ANOVA yielded a p-value of 0.010 ($p < 0.05$), indicating significant differences among groups. Among the test formulations, F3 stood out with a wound closure rate of 81.25 ± 7.76 %, ranking third and nearly matching the healing performance observed in both control groups. Although the differences between F3 and the normal and diabetic controls were not statistically significant, F3 exhibited a marked improvement over the placebo control (K3), which recorded the lowest healing percentage of 61.67 ± 11.30 %. Additionally, F1 and F2 demonstrated promising wound healing effects, reflecting positive therapeutic potential. Despite the lack of statistical significance in comparison to controls, these findings indicate that hydrogels incorporating rambutan leaf extract may promote wound repair more effectively than placebo. Optimisation of the extract concentration within the formulations could further enhance their healing capacity, possibly surpassing the efficacy of standard treatments in both normal and diabetic conditions.

Discussion

The current study demonstrated a commendable extraction yield of 25.44 % from *Nephelium lappaceum* L (rambutan) leaves, indicating efficient re-

covery of bioactive constituents, which aligns with the known efficacy of 70 % ethanol in extracting both polar and semi-polar compounds such as tannins and flavonoids from plant matrices.

The suitability of this solvent concentration for flavonoid and tannin extraction is corroborated by the work of Chigurupati, whose findings support the preferential solubility profiles of such phytochemicals.[25] The qualitative phytochemical screening confirmed the presence of tannins and flavonoids; the tannins were characterised by the formation of dark blue complexes upon reaction with ferric chloride and the flavonoids by the reddish-yellow colouration with sodium hydroxide. Quantitatively, the extract contained 2.94 % tannins and 5.73 % flavonoids. These values fall within therapeutic ranges commonly reported for topical applications, signifying meaningful pharmacological potential.[25]

From a mechanistic standpoint, tannins contribute to wound healing through antimicrobial and astringent effects forming protein tannin complexes that can inhibit microbial proliferation and support haemostasis.[26] Meanwhile, flavonoids are known to attenuate inflammation by modulating key signalling pathways such as NF-κB and MAPK, reducing pro-inflammatory cytokines and enhancing tissue regeneration during the proliferative phase of healing.[27] Together, these compounds likely synergise to accelerate re-epithelialisation, collagen deposition and neovascularisation hallmarks of effective healing. When compared to widely studied medicinal plants such as *Centella asiatica* and *Moringa oleifera*, rambutan leaf extract exhibits competitive concentrations of bioactive phytochemicals, suggesting comparable therapeutic efficacy.[28] However, comprehensive pharmacodynamic validation, including molecular-level analyses, remains essential to fully establish its *in vivo* relevance.

A key innovation of this study was the embedding of rambutan leaf extract into a sprayable thermosensitive hydrogel comprising sodium alginate, Poloxamer 407 and Poloxamer 188. The resulting formulation was homogeneous and stable, with physicochemical properties suitable for topical application. The pH values ranged from 4.52 to 5.03, closely aligning with the skin's physiological pH (approximately 4.5 - 6.5), which is critical to minimise irritation and enhance user comfort. Formulation F3, containing 7 % extract, showed the greatest spreadability with a value of 6.68 ± 0.16 cm, indicating that this hydrogel can be applied more easily and covers a larger area compared to the other formulations, which ranged from 5.20 to 6.68 cm.[29] This is a practical advantage, enabling thorough and uniform coverage of wound surfaces. The gelation time, observed between 70.67 and 88.67 seconds, supported rapid sol-to-gel transformation at body temperature, ensuring that the hydrogel solidifies promptly upon application to minimise runoff and improve bioadhesion.[18]

The swelling index, between 201.29 % and 206.86 %, falls within the ideal range of 200–500 %, indicating adequate ability to absorb exudate while maintaining a moist healing environment, which is crucial for cellular activities such as proliferation and migration.[30] Although the viscosity values 892.70–995.07 cP are somewhat lower than those of conventional hydrogels often exceeding 2,500 cP, this reduced viscosity appears to be a strategic design choice. It likely represents a trade-off to retain sprayability, a key feature while still providing sufficient cohesiveness and physical stability. Balancing these rheological properties is essential for delivering an effective, user-friendly wound dressing.

Importantly, *in vivo* wound healing studies in diabetic rats illustrated that the formulations F1–F3 significantly promoted wound closure, with F3 achieving 81.25 % closure by day 21. This performance nearly matched the normal control 84.00 % and substantially outperformed the reference drug group 61.67 %. Statistical analysis confirmed the significance of these differences $p = 0.010$, $p < 0.05$, supporting the hypothesis of extract-driven, concentration-dependent enhancement of wound healing.

This potent efficacy may be attributed to a combination of the rambutan leaf extract's bioactivities such as antimicrobial, anti-inflammatory, astringent effects and the sustained, localised release provided by the thermoresponsive hydrogel.[12] The formulation's sprayable nature enhances practical application, reducing direct contact with open wounds, minimising infection risk and increasing patient compliance.[16] Such a delivery mechanism is consistent with modern strategies that emphasise targeted, minimally invasive and patient-centric therapeutic approaches.

In the broader landscape of wound healing technologies, sprayable thermosensitive hydrogels

are emerging as a transformative platform. For instance, systems based on Pluronic F127 or Poloxamer 407 have been shown to deliver antimicrobial agents effectively and form *in situ* gels at physiological temperature.[16] Similarly, formulations incorporating poloxamer-lysine-DOPAC (PFLD) demonstrated rapid gelation, strong mechanical integrity and pronounced antibacterial and antioxidant capabilities, achieving wound shrinkage rates near 100 % by day 14.[31] Those findings support and contextualise our strategy of combining a thermosensitive carrier with bioactive phytopharmaceuticals. Moreover, reviews on thermosensitive hydrogel dressings highlight their adaptability to irregular wound geometries, capacity for sustained delivery of therapeutic agents and maintenance of a moist microenvironment conducive to cellular regeneration.[32] These advantages reinforce the translational potential of our formulation, particularly for chronic wounds such as those prevalent in diabetic patients.

Nevertheless, presented study has limitations. The sample size was modest n = 4 per group, which may limit statistical power and generalisability. The duration of wound monitoring 21 days permits only short-term efficacy assessment, leaving long-term outcomes such as scar formation and remodelling unaddressed. Additionally, histological and biochemical analyses such as quantification of biomarkers like VEGF as angiogenesis, IL-6 or TNF-α as inflammation, hydroxyproline as collagen deposition and ROS levels were not conducted, limiting mechanistic insight.

Future research should address these gaps by incorporating larger animal cohorts, extending follow-up periods to assess scar quality and healing phases and including histopathological and molecular assays to map underlying mechanisms such as anti-inflammatory signalling, antioxidant activity, angiogenesis. Additionally, pharmacokinetics of extract release, stability studies and optimisation of hydrogel composition for release kinetics should be pursued. Finally, clinical trials will be essential to confirm safety, tolerability, efficacy and application feasibility in human diabetic wound care settings.

Conclusion

The study demonstrated that rambutan leaf extract, rich in tannins and flavonoids, can be effectively formulated into a sprayable thermosensitive hydrogel. The F3 formulation showed the highest wound healing activity (81.25 %) in diabetic rats, resembling the activity of the normal control group. The hydrogel met acceptable physical criteria for topical use, including appropriate pH, spreadability, gelation time and viscosity. These findings suggest that rambutan leaf extract in a thermoresponsive hydrogel offers promising potential as a natural, effective and user-friendly alternative for diabetic wound care. Further research is needed to confirm long-term efficacy and underlying mechanisms.

Ethics

All animal procedures in this study were reviewed and approved by the Institutional Animal Ethics Committee of Universitas Ahmad Dahlan (KEP UAD), with the approval reference number 012307140, dated 7 August 2023.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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