

FORMULATION AND EVALUATION OF ETHOSOMAL GEL OF CARICA PAPAYA AND BRYOPHYLLUM PINNATUM LEAF EXTRACTS FOR THE EFFECTIVE MANAGEMENT OF WOUND HEALING

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ABSTRACT

Background: Plant-derived extracts are being investigated as potential sources of bioactive compounds for topical wound management. Ethosomes, composed of phospholipids and a relatively high proportion of ethanol, offer a vesicular delivery approach that may improve the transport of incorporated constituents across skin barriers.

Objective: The present study aimed to formulate and evaluate an ethosomal gel containing *Carica papaya* and *Bryophyllum pinnatum* leaf extracts and investigate its physicochemical characteristics, release and permeation behavior, antimicrobial activity, preliminary irritation potential, and wound-healing efficacy.

Methods: Ethosomes containing the two herbal extracts were prepared by the thin-film hydration method using lecithin concentrations of 1.0–2.0%, ethanol volumes of 10–20 mL, and a constant cholesterol concentration of 0.2%. The selected dispersion was incorporated into a Carbopol 980NF gel base at 0.75% w/w. Vesicle size, polydispersity index (PDI), zeta potential, morphology, and entrapment efficiency were evaluated. The gel was characterized for pH, extract content, spreadability, viscosity, In vitro release, ex vivo permeation through porcine skin, antimicrobial activity, and irritation potential using the hen's egg test–chorioallantoic membrane (HET-CAM) assay. Wound-healing activity was investigated using an excision-wound model in Wistar rats, with untreated wounds and Betadine ointment serving as comparators.

Results: The optimized ethosomal dispersion exhibited a mean vesicle size of 189.3 ± 2.55 nm, a PDI of 0.6436 ± 0.03 , a zeta potential of -21.79 ± 0.75 mV, and an entrapment efficiency of $84.23 \pm 2.15\%$. The formulated gel had a pH of 6.8, extract contents of 90.95% for *C. papaya* and 88.65% for *B. pinnatum*, spreadability of $33.65 \text{ g}\cdot\text{cm/s}$, and viscosity of $39,435 \text{ cP}$. At 24 h, cumulative In vitro release reached $91.26 \pm 1.86\%$ and $94.18 \pm 1.93\%$ for the respective extracts, while ex vivo permeation reached $63.28 \pm 1.62\%$ and $67.42 \pm 1.71\%$. The gel produced inhibition zones of 18.6 ± 0.6 mm against *Staphylococcus aureus* and 16.8 ± 0.5 mm against *Bacillus subtilis*. Its HET-CAM irritation score was 0.38 ± 0.11 . In the rat excision-wound model, the formulation produced $95.8 \pm 2.0\%$ wound contraction by day 15, compared with $82.8 \pm 3.0\%$ in untreated wounds and $97.2 \pm 1.6\%$ with Betadine ointment. The epithelialization period was 14.7 ± 0.6 days for the herbal ethosomal gel.

Conclusion: The combined herbal ethosomal gel demonstrated favorable formulation characteristics, measurable antimicrobial activity, low acute irritation potential in the HET-CAM assay, and enhanced wound closure in the experimental model. These findings support further investigation of the formulation, including standardized phytochemical characterization, statistical validation, dermal safety assessment, and controlled efficacy studies.

KEYWORDS: *Carica papaya*; *Bryophyllum pinnatum*; ethosomes; herbal gel; wound healing; topical drug delivery; antimicrobial activity; skin permeation; wound contraction.

INTRODUCTION

Wound healing is a dynamic and highly regulated biological process that restores tissue integrity following injury. The skin serves as a protective barrier against microorganisms, chemical agents, physical damage, and excessive water loss. Disruption of this barrier initiates a series of coordinated cellular and biochemical responses involving hemostasis, inflammation, proliferation, and remodeling. Although these phases overlap, each contributes distinct functions to the restoration of tissue architecture and physiological integrity. Any disturbance in these processes may prolong healing, increase susceptibility to infection, or result in chronic wounds and abnormal scar formation [1-3].

The inflammatory phase is essential for removing damaged tissue and initiating repair; however, prolonged inflammation and excessive production of reactive oxygen species can damage viable cells and interfere with tissue regeneration. The proliferative phase involves fibroblast migration, extracellular matrix deposition, angiogenesis, granulation tissue formation, and re-epithelialization. During remodeling, collagen organization and tissue strength progressively improve. Consequently, effective wound-management strategies should support a favorable local environment while minimizing additional tissue damage and microbial complications [4-6].

Conventional wound-care preparations, including antiseptics, dressings, and other topical products, remain important components of wound management. Nevertheless, formulation performance depends on the nature of the wound, its severity, the presence of infection, and the characteristics of the applied product. These considerations have encouraged

investigations into plant-derived preparations containing phytochemicals that may exhibit antioxidant, anti-inflammatory, or antimicrobial properties. However, such activities must be established experimentally, and herbal products should not be presumed effective or safe solely because of their traditional use [7-10].

Carica papaya L., belonging to the family Caricaceae, is a medicinally investigated plant containing diverse secondary metabolites. Its leaves have attracted scientific interest because of their potential biological activities. Depending on the extraction method and source material, leaf extracts may contain phenolic compounds, flavonoids, tannins, and other constituents that warrant investigation in wound-related applications. The biological effects of these constituents depend on their chemical composition, concentration, stability, and availability at the site of application [11-12].

Bryophyllum pinnatum (Lam.) Oken, also known in botanical literature as *Kalanchoe pinnata*, is another plant investigated for its phytochemical and pharmacological properties. Its leaves may contain flavonoids, phenolic compounds, and other secondary metabolites of potential biological interest. Combining extracts of *C. papaya* and *B. pinnatum* provides an opportunity to investigate a multicomponent botanical preparation in which the overall biological response may reflect the individual constituents, their interactions, and the delivery system. However, additive or synergistic effects cannot be established without appropriate comparative experiments involving the individual extracts and their combination [13-15]. The effectiveness of a topical herbal preparation also depends on the pharmaceutical vehicle. Conventional gels provide convenient application, acceptable cosmetic characteristics, and retention at the application site. Carbopol-based polymers are frequently investigated for topical formulations because they form semisolid matrices after hydration and appropriate neutralization. Nevertheless, the incorporation of plant extracts or lipid vesicles may alter pH, viscosity, spreadability, release characteristics, and storage stability. Therefore, the final gel requires independent characterization [16-17].

Ethosomes represent a vesicular drug-delivery approach based on phospholipids and relatively high ethanol concentrations. Ethanol may influence lipid organization and skin-barrier properties, while phospholipid vesicles can provide a carrier environment for selected compounds. The performance of an ethosomal system depends on lipid concentration, ethanol content, composition, vesicle size distribution, surface properties, and the characteristics of the incorporated substances. Ethosomal delivery may improve topical or transdermal transport under suitable conditions, but enhanced skin penetration must be demonstrated experimentally rather than assumed from vesicle formation alone [18-20].

In the present investigation, ethosomes containing ethanolic extracts of *C. papaya* and *B. pinnatum* leaves were prepared using a thin-film hydration method and incorporated into a Carbopol 980NF gel. The formulation-development approach included variation of lecithin concentration and ethanol volume, followed by physicochemical characterization of the selected dispersion and the final gel. In vitro release, ex vivo skin permeation, antimicrobial activity, and preliminary irritation potential were also investigated. Finally, wound-healing performance was evaluated in a rat excision-wound model using untreated wounds and Betadine ointment as comparators. The primary objective was to develop and characterize a combined herbal ethosomal gel and assess its preliminary pharmaceutical and wound-healing performance. The study provides an experimental basis for further investigation of this delivery system while recognizing the need for standardized extract characterization, rigorous statistical analysis, and additional safety and efficacy studies.

MATERIALS AND METHODS

Materials

Lecithin and cholesterol were procured from SD Fine-Chem Ltd., India. Polyethylene glycol, Carbopol 980NF, and ethanol were obtained from Merck, India. Ether, potassium dihydrogen phosphate, and sodium hydroxide were procured from CDH Fine Chemical, India. Extracts of *C. papaya* and *B. pinnatum* leaves were purchased from Phyto Drugs Pvt. Ltd., India. Other chemicals were of analytical grade.

Preparation of extract-loaded ethosomes

Ethosomes were prepared using the thin-film hydration technique. Lecithin was dissolved in an appropriate chloroform-containing organic solvent mixture in a clean, dry round-bottom flask. The organic solvent was removed under reduced pressure using a rotary evaporator to obtain a thin lipid film on the inner surface of the flask. The resulting film was hydrated with a preparation containing the two herbal extracts under continuous rotation at 900 rpm for 10 min at 30°C. The dispersion was subsequently sonicated to obtain a more uniform vesicular preparation. The total formulation volume was intended to be adjusted to 100 mL. The prepared formulation was subsequently characterized for vesicle size, polydispersity index, zeta potential, morphology, and entrapment efficiency [21-23].

Characterization of ethosomes

Vesicle size, polydispersity index, and zeta potential

Vesicle size and polydispersity index (PDI) were determined using a Malvern Zetasizer Nano ZS employing dynamic light scattering. The mean vesicle size was used to characterize the nanometric dimensions of the dispersion, while PDI was used to assess the breadth of the measured size distribution. Zeta potential was recorded as an indicator of surface charge. Measurements should be reported as mean $\pm$ standard deviation, together with the number of independent batches and technical replicates [24-25].

Vesicle morphology

Transmission electron microscopy (TEM) was used to examine vesicle morphology. A drop of the sample was deposited onto a carbon-coated copper grid and allowed to stand for 15 min. The sample was negatively stained using 1% aqueous phosphotungstic acid and air-dried before imaging. Scanning electron microscopy (SEM) was performed using a JEOL JSM-6360 instrument. Samples were spread onto glass slides, dried, sputter-coated with gold, and examined at an accelerating voltage of 20 kV. The resulting micrographs were evaluated for particle morphology, surface appearance, and evidence of aggregation [26-28].

Entrapment efficiency

The reported analytical procedure involved treating 25 mg of ethosomal formulation with 10 mL of Triton X-100, followed by sonication for 20–30 min to disrupt the vesicles. The resulting preparation was diluted with phosphate-buffered saline at pH 7.4 and analyzed spectrophotometrically at 415 nm for *C. papaya* extract and 348 nm for *B. pinnatum* extract [29–30].

Preparation of ethosomal gel

The selected ethosomal dispersion was incorporated into a Carbopol 980NF gel base at a final polymer concentration of 0.75% w/w. Carbopol 980NF was gradually dispersed into the ethosomal suspension under continuous stirring at approximately 100–200 rpm for 10 min. The mixture was allowed to hydrate to form a consistent gel matrix. A 10% w/v aqueous solution of meglumine was then added dropwise to adjust the pH. The preparation procedure specified a target pH range of 6.0–6.5. The mixture was gently stirred until a homogeneous gel was obtained.

The experimentally reported final pH was 6.8 [31–32].

Evaluation of the ethosomal gel

pH determination

5 g of gel was dispersed in 50 mL of distilled water. The pH was measured at 25°C using a calibrated pH meter [33].

Extract content

Approximately 1 g of gel was dispersed in 10 mL of methanol and sonicated for 15 min. The resulting preparation was diluted appropriately and analyzed spectrophotometrically at 415 nm for *C. papaya* and 348 nm for *B. pinnatum*. Extract content was expressed as a percentage of the intended amount, subject to the accuracy and specificity of the analytical method [34–35].

Spreadability

Spreadability was assessed using the drag-and-slip method. Approximately 2 g of gel was placed between two glass slides, and a known weight was applied to distribute the formulation uniformly. The upper slide was connected to a pulley system, and the time required to travel a distance of 10 cm was recorded [36].

Viscosity

Approximately 50 g of gel was transferred into a 100 mL beaker without introducing air bubbles. Viscosity was measured using a Brookfield viscometer fitted with spindle number 64 at $25 \pm 1^\circ\text{C}$. Readings were intended to be obtained at rotational speeds of 10, 20, 50, and 100 rpm after stabilization. Measurements were reported as triplicates [37–38].

In vitro release study

In vitro release was investigated using a vertical Franz diffusion cell fitted with a hydrated dialysis membrane having a reported molecular-weight cut-off of approximately 12–14 kDa. The receptor compartment contained phosphate buffer at pH 6.8 and ethanol in a reported ratio of 2:3. The system was maintained at $32 \pm 0.5^\circ\text{C}$ and stirred at 100 rpm. 1 g quantity of gel was placed in the donor compartment. At predetermined intervals, samples were withdrawn from the receptor compartment and replaced with an equal volume of fresh receptor medium to maintain the specified volume. The released extract-equivalent content was estimated using UV-visible spectrophotometry [39–41].

HET-CAM irritation assessment

The preliminary irritation potential was investigated using the hen's egg test–chorioallantoic membrane assay. Fertilized White Leghorn chicken eggs, reported as 9 days old and weighing 55 ± 5 g, were incubated at $37.5 \pm 0.5^\circ\text{C}$ and relative humidity of $62.5 \pm 7.5\%$. After candling to confirm viability, a small window was created in the eggshell to expose the chorioallantoic membrane (CAM). Approximately 0.3 mL of the test formulation was applied to the exposed membrane, which was observed for 5 min for hemorrhage, vascular lysis, and coagulation [42–44]. The controls included untreated CAM, 0.9% sodium chloride, 0.1 N sodium hydroxide, and the Carbopol gel base. The onset of vascular responses was recorded and used to calculate the irritation score according to the specified scoring system. The supplied record identifies three replicates for the reported results.

Experimental animals and wound-healing evaluation

Adult male Wistar rats aged 9–11 weeks and weighing 180–250 g were used for the excision-wound study. Animals were maintained at $25 \pm 2^\circ\text{C}$ under a 12-h light–dark cycle with free access to standard pellet diet and water. The study was reported as approved by the Institutional Animal Ethics Committee of Adina Institute of Pharmaceutical Sciences, Sagar, Madhya Pradesh, under registration number 1546/PO/Re/S/11/CCSEA. The approval number and the corresponding protocol-specific approval documentation should be verified before submission.

The animals were allocated to four groups of six animals each:

Group I: Normal control for assessment of normal skin morphology.

Group II: Untreated excision-wound control.

Group III: Treatment with the optimized *C. papaya* and *B. pinnatum* ethosomal gel.

Group IV: Treatment with Betadine ointment as the reference preparation.

A full-thickness excision wound of approximately 300–500 mm² was created on the dorsal thoracic region under the reported anesthetic and aseptic conditions. The animals were monitored throughout the experimental period. The supplied record describes ether anesthesia; the anesthetic protocol should be checked against the approved animal study protocol and applicable institutional requirements. Wound area was measured on days 0, 2, 4, 6, 8, 12, and 15. Percentage wound contraction was calculated. The epithelialization period was recorded as the number of days required for complete wound closure with formation of new epithelium [45–46].

Histopathological evaluation

Wound biopsy specimens were fixed in 10% buffered formalin, dehydrated through graded alcohol, embedded in paraffin, and sectioned at 4 μm . The sections were stained with hematoxylin and eosin and examined using a Nikon E200 LED

light microscope at magnifications of $\times 10$ and $\times 40$. Histological examination was intended to assess tissue architecture and wound-repair characteristics. Specific findings concerning inflammatory-cell infiltration, granulation tissue, epithelial continuity, collagen organization, and angiogenesis should be reported only where supported by documented microscopic observations [47-48].

RESULTS AND DISCUSSION

Characterization of extract-loaded ethosomes

Vesicle size, PDI, and zeta potential

The optimized ethosomal dispersion exhibited a mean vesicle size of 189.3 ± 2.55 nm. This result indicates that the formulation produced vesicles within the nanometric range. The reported PDI was 0.6436 ± 0.03 . Although the average vesicle size was relatively small, the PDI indicates a broad size distribution rather than a highly uniform dispersion. This finding is important because a heterogeneous population may contain vesicles and aggregates with different transport, release, and storage characteristics. The measured zeta potential was -21.79 ± 0.75 mV. The negative surface charge indicates that the dispersed vesicles possessed a net negative electrokinetic potential under the measurement conditions. This may contribute to electrostatic repulsion between particles, but the magnitude alone does not prove long-term stability. Phospholipid composition, ethanol concentration, steric effects, medium composition, and storage conditions also influence vesicle stability [49].

Vesicle morphology

TEM examination reportedly showed vesicular structures with dimensions of approximately 200 nm, broadly consistent with the particle-size measurement. The observed bilayer structures support the formation of lipid-based vesicles. SEM micrographs showed predominantly spherical to slightly irregular particles with relatively smooth surfaces.

Entrapment efficiency

The developed formulation exhibited a reported entrapment efficiency of $84.23 \pm 2.15\%$. This value suggests that a substantial proportion of the measured extract content was associated with the ethosomal preparation under the reported analytical conditions. The result is promising from a formulation-development perspective because association of the extract constituents with the vesicular system may influence their distribution and release. However, both plant extracts are chemically complex mixtures, and absorbance at a single wavelength may not selectively quantify all relevant phytoconstituents.

Physicochemical evaluation of the ethosomal gel

The final gel exhibited a measured pH of 6.8. This value is within a range that may be compatible with topical application. The extract contents were 90.95% for *C. papaya* and 88.65% for *B. pinnatum*. These findings suggest recovery of most of the intended extract content under the reported analytical procedure. The spreadability was reported as 33.65 g·cm/s. This result indicates measurable spreading performance under the selected experimental conditions. The viscosity was reported as 39,435 cP. This relatively high apparent viscosity may support retention of the gel at the application site. Nevertheless, topical performance depends on the relationship between viscosity, shear rate, thixotropy, and yield behavior rather than a single viscosity value [50].

In vitro release behavior

The optimized ethosomal gel demonstrated progressive release of both herbal extracts over 24 h. The cumulative release reached $91.26 \pm 1.86\%$ for *C. papaya* and $94.18 \pm 1.93\%$ for *B. pinnatum* at the final sampling point. The reported profiles indicate that the extract-equivalent material became available in the receptor medium throughout the study. The release behavior may reflect a combination of diffusion through the hydrated gel matrix, partitioning between formulation components and the aqueous medium, and release from the vesicular structures (Figure 1).

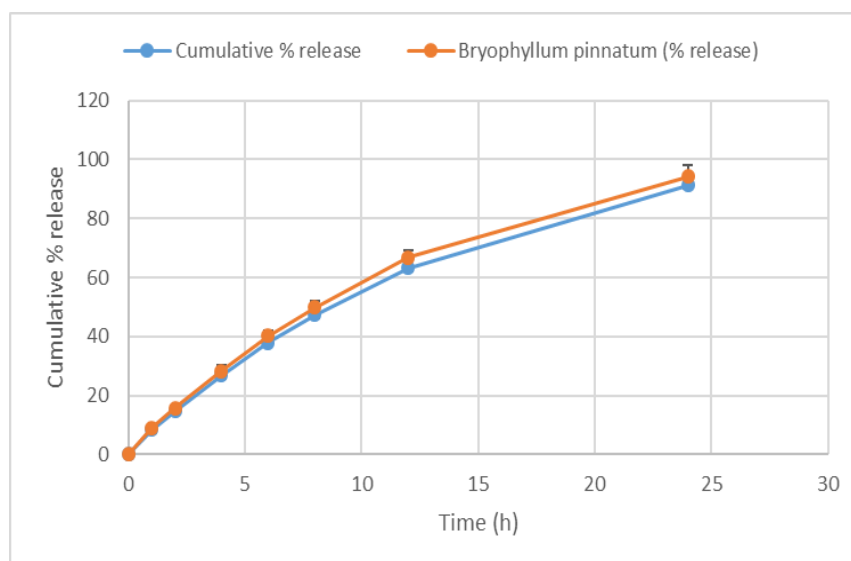


Figure 1: In vitro cumulative % release of *Carica papaya* and *Bryophyllum pinnatum* extracts (mean $\pm$ SD, n = 6)

Preliminary irritation assessment by HET-CAM

The HET-CAM assay was used to assess acute vascular responses after exposure to the test formulation. Untreated CAM and the 0.9% sodium chloride control reportedly showed no detectable hemorrhage, vascular lysis, or coagulation and had irritation scores of 0.00 ± 0.00 . The strong irritant control, 0.1 N sodium hydroxide, produced pronounced vascular responses and an irritation score of 15.82 ± 0.64 .

The Carbopol gel base exhibited an irritation score of 0.24 ± 0.08 , whereas the optimized ethosomal gel had a score of 0.38 ± 0.11 . No marked vascular changes were reported for the test formulation during the 5-min observation period.

These findings indicate low acute irritation potential in this particular assay. The close numerical values for the gel base and the ethosomal gel suggest that the addition of the herbal ethosomal dispersion did not substantially increase the observed irritation response under the tested conditions. Nevertheless, the absence of a marked CAM response does not establish that the formulation is non-irritant in every setting or safe for application to open wounds. Ethanol concentration, lipid composition, extract impurities, and repeated exposure may influence local tolerability.

Wound-healing activity in the excision model

The wound-healing potential of the optimized ethosomal gel was evaluated in a rat excision-wound model. The reported initial wound areas were comparable across the untreated, ethosomal-gel, and Betadine-treated groups, with values of 402.6 ± 12.4 , 398.8 ± 11.7 , and 401.2 ± 12.1 mm², respectively. These measurements indicate broadly similar starting wound sizes among the three wound-bearing groups. A progressive decrease in wound area was observed over the 15-day observation period. The untreated group exhibited the slowest closure, while the ethosomal-gel group demonstrated greater reduction in wound area. Betadine ointment produced the greatest reported contraction at the final observation (Figure 2).

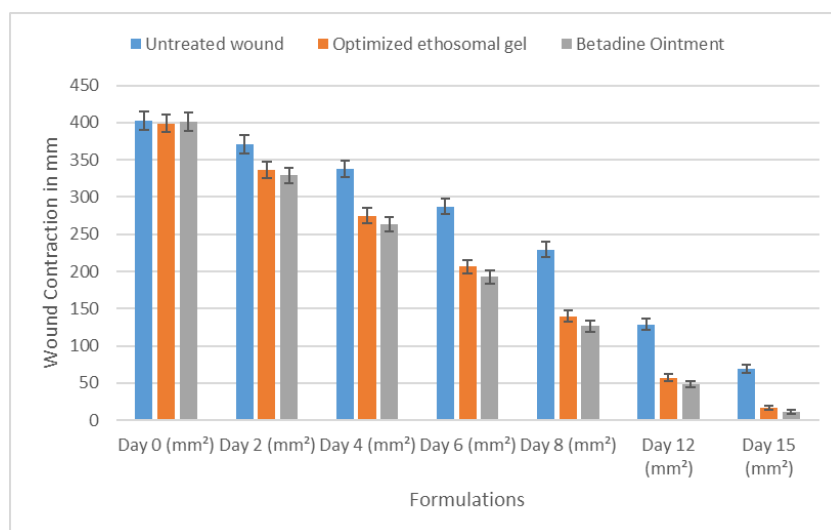


Figure 2: Effect of prepared ethosomal gel on wound area (mean $\pm$ SD, n = 6)

On day 15, the ethosomal gel achieved $95.8 \pm 2.0\%$ wound contraction, compared with $82.8 \pm 3.0\%$ in the untreated group and $97.2 \pm 1.6\%$ with Betadine ointment. The numerical difference between the herbal gel and untreated treatment groups supports a favorable wound-closure response. However, statistical significance cannot be concluded without the original animal-level observations and appropriate between-group analyses. The epithelialization period was reported as 18.3 ± 0.8 days for untreated wounds, 14.7 ± 0.6 days for the optimized ethosomal gel, and 13.9 ± 0.5 days for Betadine ointment.

CONCLUSION

The present study describes the formulation and preliminary evaluation of an ethosomal gel containing *Carica papaya* and *Bryophyllum pinnatum* leaf extracts for potential topical wound management. The prepared ethosomes exhibited a mean vesicle size of 189.3 ± 2.55 nm, a PDI of 0.6436 ± 0.03 , a zeta potential of -21.79 ± 0.75 mV, and a reported entrapment efficiency of $84.23 \pm 2.15\%$. Incorporation into a Carbopol 980NF gel produced a semisolid formulation with a pH of 6.8, extract contents of 90.95% and 88.65%, spreadability of 33.65 g·cm/s, and viscosity of 39,435 cP. The formulation demonstrated substantial cumulative *In vitro* release and measurable *ex vivo* permeation of both extracts over 24 h. It also produced inhibition zones against the tested bacterial and fungal organisms and showed a low irritation score in the HET-CAM assay. In the rat excision-wound model, the formulation achieved $95.8 \pm 2.0\%$ wound contraction by day 15 and an epithelialization period of 14.7 ± 0.6 days, compared with $82.8 \pm 3.0\%$ contraction and 18.3 ± 0.8 days, respectively, in untreated wounds. Betadine ointment produced slightly higher wound contraction and a shorter epithelialization period than the herbal formulation.

Collectively, the results indicate that the combined herbal ethosomal gel merits further investigation as a topical wound-care candidate. Nevertheless, the findings do not establish clinical effectiveness, synergistic activity between the extracts, or superiority of ethosomal delivery over conventional herbal gels. Future work should include improved vesicle-size uniformity, validated quantitative phytochemical analysis, complete factorial optimization and statistical reporting, controlled comparisons with individual extracts and blank carriers, detailed histopathological assessment, and appropriate dermal safety and stability studies. Carefully designed follow-up investigations will be necessary to establish

reproducibility, clarify the mechanisms underlying the observed wound-healing response, and determine whether the formulation offers a meaningful advantage over established topical preparations.

DECLARATIONS

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REFERENCES

1. Araújo ERD, Xavier-Santos JB, da Silva VC, de Lima JBF, Schlamb J, Fernandes-Pedrosa MF, et al. Gel formulated with Bryophyllum pinnatum leaf extract promotes skin wound healing in vivo by increasing VEGF expression: a novel potential active ingredient for pharmaceuticals. *Front Pharmacol*. 2022;13:1104705. doi:10.3389/fphar.2022.1104705.
2. Izundu MI, Anyamene CO, Ogbonna EAK, Umeh OR, Nwiyi IU. Inhibitory effects of Azadirachta indica (neem) and Bryophyllum pinnatum (Oda Opue) leaves extracts on Staphylococcus aureus isolated from infected wound samples. *J Adv Med Pharm Sci*. 2021;18-26. doi:10.9734/jamps/2021/v23i630241.
3. Oluchi OF, Ngozika WG, Godwin NE. Phytochemical and antimicrobial activities of Bryophyllum pinnatum and Vernonia amygdalina leaves extracts on selected microbial isolates from wound infection. *J Adv Microbiol*. 2019;1-14. doi:10.9734/jamb/2019/v15i330090.
4. Gupta C, Sahu GK, Parashar AK, Singh K, Bukke SPN, Udom GJ. Novel curcumin floating tablets for spatial delivery in peptic ulcer. *Biomed Res Int* [Internet]. 2025;2025(1):6622146. Available from: <http://dx.doi.org/10.1155/bmri/6622146>
5. Parashar AK, Saraogi GK, Shrivastava V, Bagri R, Tyagi LK, Sethi VA, et al. Development of Angiopep-2 targeted dendrimer-based nanotheranostic system for enhanced temozolomide delivery to glioblastoma multiforme. *Bull Natl Res Cent* [Internet]. 2025;49(1). Available from: <http://dx.doi.org/10.1186/s42269-025-01309-3>
6. Obioma A, Chikanka AT, Dumo I. Antimicrobial activity of leaf extracts of Bryophyllum pinnatum and Aspilia africana on pathogenic wound isolates recovered from patients admitted in University of Port Harcourt Teaching Hospital, Nigeria. *Ann Clin Lab Res*. 2017;5(3). doi:10.21767/2386-5180.1000185.
7. Beshel JA, Ujong GO, Okon IA, Ejim CI, Idam B, Gekpe CG. Hepatoprotective potentials of Bryophyllum pinnatum ethanolic leaf extract on adrenaline-induced liver damage in Wistar rats. *J Pharm Res Int*. 2025;37(10):35-48. doi:10.9734/jpri/2025/v37i107752.
8. Jain PK, Parashar AK, Shrivastava V. A review on exploring the health benefits and antioxidant properties of bioactive polyphenols. *Discov Food* [Internet]. 2025;5(1). Available from: <http://dx.doi.org/10.1007/s44187-025-00637-7>
9. Saini K, Parashar AK, Sethi VA. Nanotechnology in psoriasis management: A new frontier in drug delivery. *Curr Nanomed* [Internet]. 2025;16. Available from: <http://dx.doi.org/10.2174/0124681873413875251111055219>
10. Akinterinwa ET, Oladejo BO, Oladunmoye MK. Antibacterial, antioxidant, and phytochemical properties of Bryophyllum pinnatum (Lam.) leaf extracts against pathogenic bacteria. *J Vocat Health Stud*. 2025;9(1):54-63. doi:10.20473/jvhs.v9.i1.2025.54-63.
11. Parashar AK, Hardenia A, Bhide P, Dwivedi SK, Chaturvedi P, Khan A. Nanozymes: The emerging frontier in catalytic nanomaterials and their therapeutic applications. *Recent Adv Drug Deliv Formul* [Internet]. 2026;20. Available from: <http://dx.doi.org/10.2174/0126673878406314251127055108>
12. Suryawanshi S, Kumar A, Deshmukh D, Jain A, Tiwari A, Vaishya BP, et al. Phytochemical screening and antimicrobial activity of Bryophyllum pinnatum leaf extract. *World J Biol Pharm Health Sci*. 2025;22(1):482-6. doi:10.30574/wjbphs.2025.22.1.0301.
13. Dantani M, Rabe AM, Dantani A. Antifungal activity of aqueous and ethanolic extracts of Bryophyllum pinnatum against pathogenic fungi in Sokoto State, Nigeria. *USci*. 2025;4(1):200-6. doi:10.56919/usci.2541.020.
14. Parashar AK, Saini K, Sethi VA, Gupta C. A review on current challenges and emerging therapies in psoriasis management. *Rev Recent Clin Trials* [Internet]. 2025;20. Available from: <http://dx.doi.org/10.2174/0115748871393960250912053926>
15. Malik Damani MY, Kakadiya J. QbD-driven development and In vitro evaluation of an ethosomal gel containing Jatropha curcas seed extract. *J Nat Remedies*. 2026;1065-80. doi:10.18311/jnr/2026/54295.
16. Rajoo SS, Huri HZ, Halim AS, Shafiee MN, Ahmad A, Mat Saad AZ. Wound healing potential of Elaeis guineensis extract: histopathological and biochemical evaluation. *J Ethnopharmacol*. 2021;275:113960.
17. Parashar AK, Hardenia A, Dwivedi SK, Saraogi GK, Hardenia S. Next-generation nucleic acid delivery: A review of nanobiosystem design and applications. *Curr Gene Ther* [Internet]. 2026;26(3):1-19. Available from: <http://dx.doi.org/10.2174/0115665232367377250519114910>
18. Agada FO, Ezeonwumelu J, Okeke NN, Ugochukwu A, Ezeani EU. In vitro antioxidant and antidiabetic activities of bioactive fractions from Carica papaya seeds. *Phytomedicine*. 2020;69:153208.

19. Hakim L, Dinni M. Effect of Carica papaya extract on incised wound healing in Mus musculus: clinical and histological study. *Int J Pharm Res Allied Sci*. 2019;8(3):80-8.
20. Saraogi GK, Parashar AK, Yasin HKA, Ahirwar J, Kumari M. Development and evaluation of glycine conjugated polypropyleneimine dendrimers for targeted chloroquine delivery. *Discov Nano* [Internet]. 2026;21(1). Available from: <http://dx.doi.org/10.1186/s11671-026-04570-1>
21. Jayronia S, Parashar AK. Formulation, characterization, and antifungal efficacy of ketoconazole emulgel for topical delivery. *J Pharm Innov* [Internet]. 2026;21(3). Available from: <http://dx.doi.org/10.1007/s12247-026-10448-7>
22. Kolhe SR, Patil SD, Bansode SG, More S, Deshmukh VN. Formulation and evaluation of polyherbal ointment and its wound healing activity. *Int J Pharm Sci Res*. 2018;9(7):2784-93.
23. Parashar AK, Saraogi GK, Jain PK, Kurmi B, Shrivastava V, Arora V. Polymer-drug conjugates: revolutionizing nanotheranostic agents for diagnosis and therapy. *Discov Oncol* [Internet]. 2024;15(1):641. Available from: <http://dx.doi.org/10.1007/s12672-024-01509-9>.
24. Zhang A, Hussain SA, Alrubie TM, Jiang R. Nanofibrous membranes loaded with bupivacaine and Carica papaya extract for pain management and wound healing in postoperative wounds. *Mater Sci Pol*. 2024;42(2):143-59. doi:10.2478/msp-2024-0019.
25. Parashar AK, Tyagi LK, Arora V. Histotripsy: A promising modality for cancer treatment. *Curr Cancer Ther Rev* [Internet]. 2025;21(7):1030–40. Available from: <http://dx.doi.org/10.2174/0115733947330950240906075443>
26. Mohamed MSN, Kolar AB, Azim JM, Mohamed SS. Solvent-specific phytochemical extraction of Carica papaya bark: a comparative study using preliminary screening and GC-MS analysis. *Biochem Cell Arch*. 2025;25(2):2219-26. doi:10.51470/bca.2025.25.2.2219.
27. Kavimandan BR, Saraf MS. Effect of purified alkaloid (carpaine) from water extract of Carica papaya L. leaves on platelet count of carboplatin-induced thrombocytopenic Sprague-Dawley rats. *Int J Sci Res Sci Technol*. 2025;12(4):886-94. doi:10.32628/IJSRST251371.
28. Asri NAAM, Sani MSA, Othman R, Nordin NFH, Desa MNM. In vitro antibacterial activities, chemical composition and efficacy of green solvent extracts of Carica papaya seed in food model systems. *Food Res*. 2025;9(4):47-59. doi:10.26656/fr.2017.9(4).388.
29. Parashar AK, Verma KK, Kumar R, Arora V. A concise review of carbon dots and their pharmaceutical and biomedical applications. *Recent Adv Drug Deliv Formul* [Internet]. 2023;17(3):183–92. Available from: <http://dx.doi.org/10.2174/0126673878237423230919070049>
30. Herman H, Prasetyawan F, Dhafin AA, Wahdi A. Effectiveness test of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of papaya latex extract (Carica papaya L.) against Pseudomonas aeruginosa. *Jurnal Ilmiah STIKES Yarsi Mataram*. 2025;15(2):87-95. doi:10.57267/jisym.v15i2.472.
31. Sun L, Hao R, Van Van K, Tian F, Xue J. Electrically conductive hydrogels for wound healing. *Adv Wound Care (New Rochelle)*. 2025. doi:10.1177/21621918251374285.
32. Yan R, Wang Y, Li W, Sun J. Promotion of chronic wound healing by plant-derived active ingredients and research progress and potential of plant polysaccharide hydrogels. *Chin Herb Med*. 2025;17(1):70-83. doi:10.1016/j.chmed.2024.11.005.
33. Yao C, Yuan Y, Du G, Li Q, Ji Y. Chinese herbal medicine-inspired construction of multi-component hydrogels with antibacterial and wound-healing-promoting functions. *J Mater Chem B*. 2025;13(8):2826-33. doi:10.1039/D4TB02058H.
34. Development and characterization of gelatin-based herbal hydrogels for managing infected wounds. *Indian J Fibre Text Res*. 2022;47(1). doi:10.56042/ijftr.v47i1.64918.
35. Sun H, Dong Z, Kou X, Zhao Q, Shi L, Ma Y, et al. Herbal molecule-mediated dual network hydrogels with adhesive and antibacterial properties for strain and pressure sensing. *RSC Adv*. 2023;13(9):5762-9. doi:10.1039/D3RA00546A.
36. Erdal Altıntaş Ö, Aytar Çelik P. Levam-based bioactive hydrogels containing herbal liposome in treating acute wounds. *J Bioact Compat Polym*. 2023;38(6):437-57. doi:10.1177/08839115231198528.
37. Chowdary P, Pulavarthy V, Prasad VVSR, Golagana J, Balchander V, Noothi S. Development and evaluation of tofacitinib-loaded ethosomal gel for transdermal management of rheumatoid arthritis. *J Pharm Innov*. 2026;21(3). doi:10.1007/s12247-026-10417-0.
38. Patidar M, Deshmukh N, Kukloria G, Kukloria S, Pillai S, Sonane A, et al. Development and evaluation of terbinafine-loaded ethosomal gel for enhanced transdermal delivery. *Int J Drug Deliv Technol*. 2026;16(31s). doi:10.25258/ijddt.16.31s.9.
39. Parashar AK, Tiwari A, Harsola V, Kushwaha P, Jaiswal K. A mini review on nanomedicine: Current landscape, challenges, and future directions for critical illnesses. *Curr Nanomed* [Internet]. 2026;16. Doi: <http://dx.doi.org/10.2174/0124681873444221260129091144>
40. Ismail N. Exploring the antibacterial properties of Carica papaya unripe fruit extracts on wound isolates: phytochemical analysis and susceptibility testing. *IAA J Appl Sci*. 2024;11(2):76-82. doi:10.59298/iaajas/2024/112.76.82.
41. Kumar S, Gupta SP. Formulation and evaluation of polyherbal gel containing Thunbergia erecta and Bryophyllum pinnatum extracts for wound healing activity. *Res J Pharm Technol*. 2024;5816-24. doi:10.52711/0974-360X.2024.00884.
42. Chouhan SS, Parashar AK, Mahajan T, Sharma Y, Saraogi GK. Intranasal drug delivery for CNS diseases: Challenges, advances, and future directions. *Curr Pharmacol Rep* [Internet]. 2026;12(1). Available from: <http://dx.doi.org/10.1007/s40495-026-00477-8>
43. Parashar AK, Sethi VA, Saraogi GK, Yasin HKA. Applications of artificial intelligence and machine learning in drug delivery. *Rev Recent Clin Trials* [Internet]. 2026;21. Available from: <http://dx.doi.org/10.2174/0115748871436192260509042652>

44. Yahaya KI, Abdullahi MA. Antibacterial activity of *Carica papaya* (leaf and seed) extracts on methicillin-resistant *Staphylococcus aureus* (MRSA) from wound. *Int J Res Publ Rev.* 2022;3(12):1399-406. doi:10.55248/gengpi.2022.31239.
45. Soib HH, Ismail HF, Yaakob H, Idris MKH, Abd Aziz A. Effect of extraction solvents on antioxidant and wound healing properties of *Carica papaya* leaves extract. *Food Res.* 2020;4(Suppl 2):76-83. doi:10.26656/fr.2017.4(S2).S03.
46. Soib HH, Ismail HF, Husin F, Abu Bakar MH, Yaakob H, Sarmidi MR. Bioassay-guided different extraction techniques of *Carica papaya* (Linn.) leaves on In vitro wound-healing activities. *Molecules.* 2020;25(3):517. doi:10.3390/molecules25030517.
47. Chetna F, Priyadarshini P. Comparative study of hydroalcoholic extracts of *Bryophyllum pinnatum* and *Macrotyloma uniflorum* for their antioxidant, antiurolithiatic, and wound healing potential. *J Appl Biol Biotechnol.* 2022. doi:10.7324/JABB.2021.100124.
48. Parashar AK, Saraogi GK, Sethi VA, Yasin HKA. Nanocarriers in Alzheimer's therapy: A comprehensive review on nanoparticulate Drug Delivery Systems. *Curr Neurovasc Res [Internet].* 2026;23(3):160–73. Available from: <http://dx.doi.org/10.2174/0115672026435071260129105648>
49. Ugwuoji ET, Okoye EL, Ezeokoli CM, Okoye PA. Comparative analysis of the antibacterial activities of leaf extracts of *Bryophyllum pinnatum* and *Newbouldia laevis* on clinical isolates from wound infection. *Asian J Plant Soil Sci.* 2022;7(1):23-32. doi:10.56557/ajopss/2022/v7i187.
50. Vijayakumar G, Sundaram GA, Kumar SP, Lakshmanan S, Krishnan M, Krishna VK. Comparison of efficacy of topical *Carica papaya* leaf extract and hemocoagulase in postoperative wound healing after therapeutic orthodontic premolar extractions: a split-mouth study. *Cureus.* 2024;16(6):e61946. doi:10.7759/cureus.61946.