Herbal Keratolytic Hydrogel Patches for Localized Foot Corn Management: Formulation Strategies, Quality by Design, And Machine Learning-Assisted Optimization

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Abstract*—Foot corns (clavi) are localized hyperkeratotic lesions that develop in response to repeated pressure and friction, commonly over bony prominences of the toes and plantar surface. Although generally non-life-threatening, they can cause pain, difficulty in walking, and reduced quality of life. Current management includes pressure redistribution, footwear modification, mechanical reduction, and topical keratolytic preparations such as salicylic acid or urea. Recurrence may occur when the underlying mechanical cause is not corrected, while inappropriate use of keratolytics can injure surrounding skin, particularly in people with diabetes or peripheral vascular disease. Hydrogel-based patches are of interest as localized delivery platforms because hydrated polymer networks can maintain intimate contact with the application site, absorb fluid, and provide a controllable matrix for the release of incorporated substances. This review discusses the rationale for investigating herbal ingredients, including papaya-derived papain, pineapple-derived bromelain, and neem extracts, in a hydrogel patch intended for localized foot corn management. The review also considers polymer selection, formulation variables, physicochemical evaluation, in-vitro release testing, skin compatibility, and comparison with marketed corn patches. Quality by Design (QbD) can structure development through a quality target product profile, risk assessment, critical quality attributes, and design-of-experiments studies. Machine learning (ML) may complement QbD by exploring multivariable relationships and predicting formulation responses, provided that datasets are sufficiently large, reliable, and experimentally validated. Importantly, evidence supporting herbal hydrogels for wound healing or general skin delivery does not establish clinical keratolytic efficacy against foot corns. Direct studies of corn-specific keratin reduction, local safety, and clinical outcomes are still required. A herbal keratolytic hydrogel patch is therefore a promising research concept, but its efficacy and safety remain to be demonstrated.

***Index Terms*—foot corn; clavus; hyperkeratosis; herbal extract; papain; bromelain; neem; hydrogel patch; topical drug delivery; Quality by Design; machine learning.**

I. INTRODUCTION

Foot corn, also known as clavus or heloma, is a focal area of thickened skin that develops as an adaptive response to repeated mechanical pressure and friction. Unlike a diffuse callus, a corn is usually well circumscribed and may contain a central keratin plug that produces pain when pressure is applied. Common sites include the dorsal surfaces of toes, interdigital areas, and plantar pressure-bearing regions. Poorly fitting footwear, foot deformities, altered gait, prolonged standing, and repetitive loading can contribute to lesion formation [1–3].

The primary treatment principle is to reduce the mechanical force responsible for the lesion. Footwear modification, protective padding, orthoses when indicated, and professional mechanical reduction are commonly used. Keratolytic preparations containing salicylic acid or urea may help soften or remove thickened keratin. However, topical keratolytics must be used carefully because irritation or injury to adjacent healthy skin can occur. People with diabetes,

peripheral neuropathy, or impaired peripheral circulation should seek professional advice rather than self-treating corns with acidic preparations [2,3].

Hydrogels are three-dimensional hydrophilic polymer networks capable of retaining substantial quantities of water while maintaining a coherent structure. In topical delivery and wound-dressing research, hydrogels have been investigated for their moisture-retaining properties, conformability, and ability to incorporate and release bioactive compounds [4–6]. A patch format may also help maintain localized contact and reduce displacement of a formulation during daily activity. These properties provide a formulation rationale for exploring a hydrogel patch for foot corn management; they do not, by themselves, prove that a patch can remove a corn or prevent recurrence.

The proposed research concept combines herbal bioactive materials, hydrogel technology, QbD, and ML-assisted optimization. The approach is intended to produce a localized dosage form with reproducible physical properties and controlled release. This article critically reviews the scientific basis and development requirements, while distinguishing established evidence from hypotheses that require direct experimental testing.

II. REVIEW APPROACH AND SCOPE

This manuscript is a narrative review prepared from the supplied B.Pharm project report and a targeted search of relevant scientific and regulatory sources. The topics covered include clinical background of corns, topical keratolytic management, hydrogel delivery, plant-derived bioactives, formulation evaluation, QbD, and ML-assisted formulation development. It is not presented as a PRISMA systematic review: a fully reproducible database search, duplicate screening, independent study selection, and formal risk-of-bias assessment have not been completed. For a journal requiring a systematic review, the authors should conduct and report a formal search in databases such as PubMed/MEDLINE, Scopus, and Web of Science, including exact search strings, dates, eligibility criteria, screening flow, and reasons for exclusion.

III. FOOT CORN: PATHOPHYSIOLOGY, TYPES, AND RISK FACTORS

3.1 Pathophysiology

Repeated pressure and friction stimulate epidermal adaptation and increased keratin accumulation in the stratum corneum. In a corn, this response is concentrated in a small area, often above a bony prominence. The central keratin core may press into deeper tissue and cause pain, especially during standing or walking. The lesion is therefore a manifestation of abnormal local mechanical loading rather than simply an isolated excess of keratin [1,2].

3.2 Common clinical forms

- Hard corn: a compact, dry, well-defined lesion commonly found over toe joints or other bony prominences.
- Soft corn: a macerated lesion, often occurring between toes where moisture and opposing surfaces contribute to softening.
- Seed corn: small superficial keratinized lesions, often described on the plantar surface.

Clinical assessment is important because other lesions, including plantar warts and calluses, may resemble corns. Atypical, ulcerated, infected, or persistently painful lesions require professional assessment.

3.3 Predisposing factors

- Tight, narrow, or poorly fitting footwear and high local shoe pressure.
- Toe deformities, prominent metatarsal heads, altered gait, or abnormal foot biomechanics.
- Prolonged standing, repetitive activity, and occupational or sporting pressure.
- Age-related skin changes and reduced ability to inspect or care for the feet.

A topical formulation cannot correct the underlying pressure distribution. Long-term management should therefore combine any topical treatment with measures that reduce mechanical loading.

IV.EXISTING MANAGEMENT AND UNMET NEEDS

Management generally begins with identification and correction of the source of pressure. Options include

footwear adjustment, protective padding, orthotic support, and professional paring or debridement. Topical keratolytics, particularly salicylic acid and urea preparations, are used to soften hyperkeratotic tissue. In selected cases, treatment of an underlying structural deformity may be considered. Surgery is uncommon and is generally reserved for situations in which a structural cause requires correction [1–3].

The limitations of existing approaches should be described carefully. A corn can recur if pressure or friction persists. Mechanical reduction may need to be repeated. Keratolytic agents can cause irritation or damage to surrounding skin if applied incorrectly. The risk-benefit assessment is especially important in people with diabetes, neuropathy, or peripheral vascular disease; self-treatment with salicylic-acid corn products is generally discouraged in these groups [3].

A localized patch could potentially improve placement accuracy and reduce spreading of a formulation beyond the target area. A hydrogel matrix may provide a hydrated contact layer and support release of an incorporated active. These are formulation advantages to be tested, not evidence that the patch is superior to marketed products or standard care.

V. HERBAL BIOACTIVES RELEVANT TO THE PROPOSED FORMULATION

5.1 Papaya-derived papain

Papain is a proteolytic enzyme obtained from papaya (Carica papaya). Its ability to hydrolyse proteins provides a mechanistic reason to investigate it in formulations intended to act on protein-rich biological material. However, the stratum corneum is a complex structure in which keratin is organized with lipids and other components. General proteolytic activity does not establish selective, safe, or clinically meaningful removal of a foot corn. Enzyme activity, stability during extraction and storage, compatibility with the polymer matrix, and effects on healthy skin must be measured.

5.2 Pineapple-derived bromelain

Bromelain is a mixture of proteolytic enzymes obtained from pineapple (Ananas comosus), particularly the stem and fruit. Its proteolytic properties make it a candidate for exploratory formulation research. As with papain, activity against a laboratory protein substrate cannot be assumed to predict keratolysis in human skin. The selected extract should be standardized using a suitable activity assay and monitored during formulation and stability testing.

5.3 Neem (Azadirachta indica)

Neem is a medicinal plant investigated for several biological properties, including antimicrobial and anti-inflammatory activities in different experimental settings. These properties may be relevant to the broader skin-care profile of a formulation, but they do not establish neem as a keratolytic agent. If neem is included, the rationale should be clearly defined and its phytochemical profile, microbial quality, compatibility, and skin tolerability should be assessed.

5.4 Evidence gap and selection criteria

The available literature on plant-containing hydrogels largely concerns wound dressings, skin regeneration, antimicrobial effects, or general topical delivery [5,6]. Such evidence is adjacent to, but not equivalent to, evidence for corn treatment. Direct studies demonstrating that papain-, bromelain-, or neem-containing hydrogel patches safely reduce corn thickness or keratin burden were not established by the sources reviewed for this manuscript. Ingredient selection should therefore be treated as a hypothesis-driven research decision.

- Botanical identity, plant part, extraction solvent, extraction method, and batch traceability.
- Quantification of relevant chemical markers or enzyme activity.
- Microbial limits, pesticide/heavy-metal risk, residual solvent control, and stability.
- Compatibility with the polymer, pH, preservatives, backing membrane, and release liner.
- In-vitro activity against a relevant keratin or protein substrate, followed by skin-safety evaluation.

VI. HYDROGEL PATCH TECHNOLOGY FOR LOCALIZED TOPICAL DELIVERY

Hydrogels consist of hydrophilic polymer chains connected through physical or chemical crosslinks.

Their water-rich structure can support swelling, conformability, and incorporation of water-soluble or dispersed actives. For topical delivery, relevant design properties include hydration, adhesion or contact maintenance, mechanical strength, drug or marker release, and compatibility with skin [4–6].

A patch intended for corn management may include an active-containing hydrogel layer, a backing membrane, and a removable release liner. The backing can provide mechanical support and may limit moisture loss, depending on its composition. The release liner protects the contact surface during storage and is removed before application. A suitable patch should remain intact during handling, fit the intended anatomical site, and permit removal without causing unnecessary trauma.

6.1 Candidate polymers and excipients

The supplied project report identifies Carbopol 934 or hydroxypropyl methylcellulose (HPMC) as candidate hydrogel-forming polymers. Carbopol can provide viscosity and gel structure after appropriate dispersion and neutralization. HPMC is a cellulose-derived polymer used as a thickener and film-forming material. Other polymer systems, such as polyvinyl alcohol or carboxymethyl cellulose, may be considered where justified by the desired mechanical and release properties [5,6,8].

Glycerin may function as a humectant and plasticizer. Propylene glycol may function as a cosolvent and, depending on concentration and formulation, a penetration-enhancing excipient. Distilled water serves as the aqueous vehicle. Preservatives and pH-adjusting agents should be selected only after compatibility and safety assessment. The final composition must be established experimentally rather than assumed from a generic recipe.

6.2 Proposed formulation architecture

- Hydrogel matrix: selected polymer or polymer blend.
- Herbal active phase: characterized extract or enzyme preparation.
- Plasticizer/humectant: for flexibility and moisture management.
- Vehicle and processing aids: purified water and compatible excipients.
- Backing membrane and release liner: for handling, protection, and application.

The target pH should be justified by active stability, polymer performance, and intended skin contact. A pH value should not be selected solely because it is commonly used in other topical products.

VII. PROPOSED MECHANISM AND CRITICAL SCIENTIFIC CONSIDERATIONS

The proposed mechanism is localized hydration of the thickened area combined with release of a selected herbal active from the hydrogel matrix. Hydration may soften the stratum corneum. If an enzyme-containing extract is used, proteolytic activity may contribute to degradation of accessible protein substrates under suitable conditions. The magnitude and selectivity of this effect in a foot corn are unknown and require direct testing.

A scientifically valid mechanism study should distinguish (i) hydration-related softening, (ii) enzyme-mediated substrate degradation, (iii) physical removal during washing or controlled abrasion, and (iv) nonspecific tissue irritation. A reduction in mass or opacity alone is not sufficient evidence of selective keratolysis. Testing should include blank hydrogel, active-free vehicle, active-containing formulation, and an appropriate reference comparator. Any ex-vivo skin work must use an ethically and scientifically justified model.

The patch should not be described as clinically effective, safer, or superior until supported by appropriate safety and efficacy studies. In particular, the phrase 'fewer side effects than synthetic agents' should be avoided unless comparative safety data are available.

VIII.QUALITY BY DESIGN FOR FORMULATION DEVELOPMENT

Quality by Design is a systematic, science- and risk-based approach to pharmaceutical development. ICH Q8(R2) describes pharmaceutical development principles, including product and process understanding, design space, and control strategy [9]. In the proposed patch, QbD can connect the intended use and quality target product profile (QTPP) with formulation variables, manufacturing conditions, and measurable critical quality attributes (CQAs).

8.1 Quality target product profile

The QTPP should define the intended product as a localized hydrogel patch for application to a corn under controlled conditions. Candidate quality targets include uniform dimensions, adequate flexibility, suitable pH, reproducible active or marker content, acceptable adhesion/contact, controlled moisture behaviour, appropriate release, microbial quality, and stability. Numerical acceptance limits should be set using development data, safety considerations, and relevant standards; they should not be invented before testing.

8.2 Critical quality attributes

- Appearance, dimensions, thickness, mass uniformity, and surface uniformity.
- pH, moisture content, swelling index, and moisture loss.
- Folding endurance, tensile properties, and handling integrity.
- Adhesion or contact performance and ease of removal.
- Assay of marker compound or enzyme activity and content uniformity.
- In-vitro release profile, microbial quality, and stability.

8.3 Critical material attributes and process parameters

Potential critical material attributes include polymer grade and concentration, extract quality and activity, plasticizer concentration, vehicle composition, and backing/liner properties. Potential critical process parameters include polymer hydration time, mixing speed, order of addition, temperature, deaeration, casting thickness, drying or curing conditions, and packaging. Risk assessment should rank the variables according to their possible effect on CQAs.

8.4 Design of experiments

A screening design can identify influential formulation variables. A response-surface design, such as a central composite or Box–Behnken design, can then explore interactions and curvature among selected factors. Responses may include swelling, mechanical strength, marker release, adhesion, and stability indicators. The design, factor ranges, replication, randomization, and model diagnostics should be reported. The optimized formulation must be confirmed with independent experimental batches.

IX. MACHINE LEARNING-ASSISTED OPTIMIZATION

Machine learning can be used as a decision-support tool to model relationships between formulation/process inputs and measured outputs. In a hydrogel patch project, input variables might include polymer concentration, extract concentration or enzyme activity, plasticizer level, pH, mixing conditions, and casting parameters. Outputs could include thickness, swelling, mechanical strength, adhesion, release parameters, and stability indicators. Published reviews describe the potential of ML to support formulation prediction and optimization, while emphasizing the importance of data quality, validation, and interpretability [10–12].

X. SUITABLE MODELLING WORKFLOW

1. Generate a structured dataset from planned experiments. Record formulation composition, process conditions, batch identifiers, analytical methods, and replicate measurements.
2. Clean and inspect the dataset. Document missing values, outliers, measurement uncertainty, and any excluded observations.
3. Split data into training and testing sets, or use appropriately designed cross-validation when the dataset is small. Avoid data leakage between replicate samples from the same batch.
4. Compare simple baseline models with suitable algorithms such as multiple linear regression, random forest, support vector regression, or gradient boosting.
5. Evaluate performance using appropriate metrics such as R-squared, root mean squared error, and mean absolute error. Report uncertainty and avoid relying on a single metric.
6. Interpret model behaviour using feature importance or explainability methods where appropriate.
7. Select promising conditions, prepare confirmatory batches, and compare observed results with model predictions.

A small B.Pharm laboratory dataset may be insufficient for complex deep-learning models. ML

should not be used to create a false appearance of precision. A simple, transparent model with independent experimental confirmation is preferable to an overfitted model. The model cannot replace laboratory testing, safety assessment, or clinical evidence.

XI. FORMULATION DEVELOPMENT AND EVALUATION

10.1 Preparation considerations

A general development sequence may include dispersion and hydration of the selected polymer in the vehicle, incorporation of compatible excipients, addition of a characterized herbal extract under conditions that preserve its activity, pH adjustment where appropriate, deaeration, casting into a controlled mould, and attachment or integration of backing and release-liner materials. The actual process must be optimized for the selected polymer and active. Enzyme-containing extracts may be sensitive to pH, temperature, and processing time; these factors should be investigated rather than assumed.

10.2 Physicochemical evaluation

- Visual appearance and homogeneity: assess colour, clarity/opacity, bubbles, cracks, and visible separation.
- Thickness and weight variation: measure at defined locations and across replicate patches.
- Surface pH: use a justified, reproducible method suitable for hydrated topical films.
- Swelling index: determine mass change after exposure to a defined medium and time.
- Moisture content and moisture loss: assess water retention and storage-related changes.
- Folding endurance and mechanical strength: evaluate handling and resistance to tearing.
- Adhesion/contact and removability: use a reproducible method appropriate to the intended site.
- Active/marker content: use a validated or suitably qualified analytical method; for enzymes, consider activity as well as protein content.
- Microbial quality and preservative effectiveness: assess where relevant to the aqueous formulation.
- Stability: evaluate appearance, pH, mechanical properties, active/marker content, enzyme activity where applicable, and release over time.

10.3 In-vitro release and activity studies

In-vitro release testing should use a defined apparatus, medium, temperature, sampling schedule, and analytical method. Sink conditions and membrane suitability should be justified. Release profiles may be compared using cumulative amount released per unit area and appropriate kinetic models, while recognizing that model fit does not prove a biological mechanism.

For a proposed keratolytic effect, a separate activity assay should measure degradation of a relevant protein or keratin substrate. The assay should include blank matrix, active-free extract vehicle, active-containing formulation, and a reference control. Results should be normalized appropriately and reported with replicate number, variability, and statistical analysis. Protein-substrate degradation in vitro is a preliminary mechanistic endpoint, not proof of clinical corn removal.

10.4 Skin compatibility and permeation

Skin compatibility should be assessed using an appropriate validated in-vitro or ex-vivo method and under relevant ethical and biosafety requirements. The objective for a corn patch is localized action in the thickened stratum corneum, not necessarily maximal systemic or deep-skin permeation. Therefore, excessive penetration should not automatically be interpreted as better performance. Irritation potential, effects on surrounding healthy skin, and removal-related trauma are important safety outcomes.

10.5 Comparison with a marketed corn patch

A fair comparison should use predefined and comparable conditions. Physical appearance, dimensions, thickness, flexibility, adhesion, moisture behaviour, release, and in-vitro activity may be compared where the methods are suitable for both products. If the marketed product contains a different active ingredient or has a different dosage-form design, differences must be acknowledged. Greater

in-vitro release or substrate degradation does not establish superior clinical effectiveness. Clinical superiority requires appropriately designed human studies.

XII. EVIDENCE SYNTHESIS AND RESEARCH GAPS

The literature supports the general feasibility of hydrogels as topical and wound-dressing platforms and documents growing interest in incorporating plant-derived bioactives into hydrogel matrices [4–6]. Research on natural extracts in PVA and PVA–carboxymethyl cellulose hydrogels demonstrates that extract release and material properties can be studied together [8]. These studies provide formulation concepts, but their wound-healing outcomes cannot be directly transferred to corn treatment.

Clinical and professional sources consistently describe corns as pressure-related hyperkeratotic lesions and emphasize mechanical off-loading alongside keratolytic or physical treatment [1–3]. This indicates that any topical patch is likely to be an adjunct to pressure management rather than a solution to the underlying mechanical cause.

QbD provides a defensible framework for identifying material and process variables that influence product quality [9]. ML may help model complex formulation relationships, but current literature emphasizes limitations related to dataset size, data quality, interpretability, and external validation [10–12]. For a student project, the most important contribution may be a transparent DoE dataset and a modest predictive model that is tested against new experimental batches.

The key research gap is the lack of direct, high-quality evidence establishing the safety and efficacy of a papain-, bromelain-, or neem-containing hydrogel patch specifically for foot corn management. Future work should prioritize active standardization, keratin-specific assays, skin compatibility, formulation stability, and controlled comparisons with existing treatments.

XIII. CHALLENGES AND LIMITATIONS

- Botanical extracts vary with species, plant part, geography, harvest conditions, and extraction method.
- Proteolytic enzymes may lose activity during processing or storage and may affect healthy tissue if not adequately controlled.
- Hydrogel hydration and adhesion can change with temperature, humidity, sweat, and movement at the foot site.
- A patch may not address pressure from footwear or underlying foot deformity; recurrence may therefore continue.
- In-vitro release and protein degradation tests may not predict clinical outcomes.
- Small experimental datasets limit the reliability and generalizability of ML models.
- People with diabetes, neuropathy, or peripheral vascular disease require particular caution and professional assessment.

XIV. FUTURE PERSPECTIVES

Future studies should establish a clear target product profile and select one or more standardized herbal actives based on evidence, safety, and measurable activity. Enzyme activity should be monitored during formulation development and stability studies. A staged research programme could begin with material characterization and in-vitro substrate assays, proceed to physicochemical and skin-compatibility testing, and then evaluate performance in appropriately designed preclinical or clinical studies. Pressure redistribution and footwear advice should remain part of the clinical context.

Advanced formulation strategies may include polymer blends, moisture-control layers, and packaging designed to protect sensitive bioactives. QbD and DoE can identify robust formulation ranges, while interpretable ML models may assist in selecting confirmatory experiments. Any claim of improved patient outcomes, reduced adverse effects, or superiority over marketed patches must be supported by direct comparative evidence.

XV. CONCLUSION

Herbal keratolytic hydrogel patches represent an investigational approach to localized foot corn management. Hydrogel systems offer useful formulation characteristics for topical delivery, and selected plant-derived materials may provide

biological activities worth exploring. Papain and bromelain have proteolytic properties, while neem is more appropriately considered for its reported supportive skin-related activities than as an established keratolytic. However, direct evidence for the proposed herbal hydrogel patch in foot corn treatment remains insufficient. QbD can improve systematic formulation development, and ML may support prediction and optimization when reliable data and experimental validation are available. Further research is required to demonstrate keratin-specific activity, safety to surrounding skin, stability, and clinical benefit. The formulation should therefore be described as a promising research candidate rather than a proven treatment.

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