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FORMULATION AND EVALUATION OF HERBAL ANTI-ACNE TRANSDERMAL PATCH USING SAPODILLA LEAF EXTRACT

Shridhar Das Kolekar[1], Pallavi Kashinath Bhusari*[2], Roshan Ramesh Rathod[3], Mayur Bapurao Meshram[4], Datta Balaji Giri[5]

[1,3,4]Student of Samarth Institute of Pharmacy, Belhe, Maharashtra, India.

[2]Associate Professor of Samarth Institute of Pharmacy, Belhe, Maharashtra, India.

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***Corresponding Author**
Pallavi Kashinath Bhusari
Associate Professor of Samarth Institute of Pharmacy, Belhe, Maharashtra, India.

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ABSTRACT

Acne vulgaris is one of the most prevalent chronic inflammatory skin conditions globally, affecting predominantly adolescents and young adults. Conventional pharmacological treatments, including benzoyl peroxide, retinoids, and systemic antibiotics, are often associated with adverse effects such as skin irritation, antibiotic resistance, and systemic toxicity. The increasing demand for safer, cost-effective, and patient-compliant alternatives has directed research attention toward herbal-based transdermal drug delivery systems. Sapodilla (Manilkara zapota L.), commonly known as 'Chikoo' in India, is a tropical plant whose leaves are rich in bioactive phytochemicals including tannins, saponins, flavonoids, terpenoids, and phenolic compounds that possess documented antibacterial, anti-inflammatory, and antioxidant properties. This review comprehensively examines the rationale, formulation strategies, physicochemical evaluation parameters, and therapeutic efficacy of transdermal patches incorporating sapodilla leaf extract as the primary anti-acne agent. Key aspects including extraction methods, polymer selection, permeation enhancement, in vitro and in vivo evaluation, and stability studies are critically discussed. This paper aims to provide a scientific foundation for further research and commercialization of this promising herbal transdermal system.

KEYWORDS: *Acne vulgaris, Manilkara Zapota, Sapodilla leaf extract, Transdermal patch, Herbal drug delivery, Anti-acne, Phytochemicals, Polymer matrix, Permeation enhancers.*

1. INTRODUCTION

Acne vulgaris is a multifactorial chronic inflammatory disorder of the pilosebaceous unit, characterized by comedones, papules, pustules, nodules, and cysts. It affects approximately 85% of adolescents between the ages of 12 and 24 years and persists into adulthood in a significant proportion of patients. The pathophysiology involves four primary mechanisms: increased sebum production, follicular hyperkeratinization, colonization by Cutibacterium acnes (formerly Propionibacterium acnes), and subsequent inflammatory responses mediated by cytokines and toll-like receptors.

Current treatment modalities include topical retinoids, benzoyl peroxide, azelaic acid, salicylic acid, and systemic agents such as tetracyclines, macrolides, and isotretinoin. Despite their clinical effectiveness, these agents are associated with a spectrum of adverse effects including skin dryness, photosensitivity, gastrointestinal upset, teratogenicity, and the growing concern of antimicrobial resistance. Patient non-adherence remains a critical challenge, largely attributable to the inconvenience of multiple daily applications and unpleasant side effects.

Herbal medicine has emerged as an important complementary approach to managing dermatological conditions, with several plants demonstrating significant anti-inflammatory, antibacterial, and sebum-regulating properties. Among these, Manilkara zapota (L.) P. Royen, commonly known as Sapodilla or Chikoo (Hindi/Marathi), Sapota (Kannada/Telugu), Chiku (Gujarati), belongs to the family Sapotaceae. Originating from southern Mexico and Central America, it is now widely cultivated in tropical regions including India, Sri Lanka, Thailand, and the Philippines.

The leaves of Manilkara zapota have been used in traditional medicine systems including Ayurveda and traditional folk medicine for the treatment of skin diseases, diarrhea, wounds, and inflammatory conditions. Phytochemical investigations have identified a rich repertoire of bioactive compounds including quercetin, epicatechin, lupeol, oleanolic acid, ursolic acid, tannins, and saponins, many of which possess demonstrated activity against C. acnes and inflammatory mediators.

The transdermal drug delivery system (TDDS) represents an ideal platform for herbal anti-acne therapy, offering controlled and sustained release of actives directly to the target tissue while bypassing hepatic first-pass metabolism, minimizing systemic side effects, improving patient compliance, and enabling easy termination of therapy. The development of a herbal anti-acne transdermal patch using sapodilla leaf extract therefore represents a scientifically sound and clinically promising approach.

2. BOTANICAL PROFILE

2.1 Taxonomy and Classification

Taxonomic Rank	Classification
Kingdom	Plantae
Division	Magnoliophyta
Class	Magnoliopsida
Order	Ericales
Family	Sapotaceae
Genus	Manilkara
Species	Manilkara zapota (L.) P. Royen
Common Name	Sapodilla, Chikoo, Sapota, Chiku, Naseberry, Mudapple

2.2 Vernacular Names

Language / Region	Vernacular Name
Hindi	Chikoo, Sapota
Marathi	Chikoo
Tamil	Sapotta, Chikku
Telugu	Sapota
Kannada	Sapota, Saphota
Malayalam	Shappotta
Gujarati	Chiku
Bengali	Sopheda, Sapeta
English	Sapodilla, Naseberry, Dilly
Spanish	Zapotillo, Chicozapote
Thai	Lamut

2.3 Morphology and Distribution

Manilkara zapota is an evergreen tree growing up to 30 meters in height with a dense canopy. The bark is grayish-brown and scaly, containing a milky latex. Leaves are simple, alternate, elliptic to obovate in shape, 6–15 cm in length, with a glossy dark green upper surface and pale underside. Flowers are small, bell-shaped, white, and appear axillary or in clusters. The fruit is a brown, rough-skinned berry, 4–8 cm in diameter, with a sweet, malty-flavored brown flesh containing 2–5 seeds. The plant thrives in tropical climates with temperatures of 15–35°C and is cultivated extensively in Maharashtra, Gujarat, Karnataka, Andhra Pradesh, and Tamil Nadu in India.

2.4 Traditional Medicinal Uses

In Ayurvedic and traditional Indian medicine, various parts of Manilkara zapota have been used therapeutically:

- Leaves: Applied topically for skin diseases, wounds, boils, and inflammatory conditions; decoctions used as astringent gargles for oral infections.
- Bark: Used as a febrifuge, antidiarrheal agent, and treatment for pulmonary complaints.
- Seeds: Diuretic, traditionally used in kidney stone management; seed oil applied for hair care.
- Fruit: Rich in dietary fiber, used for gastrointestinal health; antioxidant properties attributed to high tannin content.
- Latex: Applied topically for corns, warts, and as a traditional dental filling material (chicle gum).

3. PHYTOCHEMISTRY OF SAPODILLA LEAF EXTRACT

3.1 Major Phytochemical Classes

The leaves of Manilkara zapota represent a complex matrix of biologically active secondary metabolites. Comprehensive phytochemical screening and chromatographic analyses have identified the following major classes:

3.1.1 Flavonoids

Flavonoids constitute the most pharmacologically significant fraction of the sapodilla leaf extract. Identified compounds include quercetin, kaempferol, myricetin, luteolin, rutin, and naringenin. These compounds exert anti-inflammatory effects by inhibiting cyclooxygenase (COX-1 and COX-2), 5-lipoxygenase, and phosphodiesterase enzymes. Quercetin has been demonstrated to suppress NF-κB activation, thereby reducing pro-inflammatory cytokine

production including IL-1β, IL-6, and TNF-α — cytokines critically involved in acne pathogenesis.

3.1.2 Tannins

Hydrolyzable and condensed tannins are present in high concentrations in sapodilla leaves. Tannic acid and ellagic acid derivatives constitute the primary hydrolyzable tannins. Tannins exert astringent properties by precipitating skin proteins, thereby contracting skin pores and reducing sebum secretion. Their antibacterial action against C. acnes has been documented through membrane disruption and enzyme inhibition mechanisms. Additionally, tannins possess significant antioxidant properties through free radical scavenging.

3.1.3 Saponins

Triterpenoid saponins including oleanolic acid glycosides and ursolic acid derivatives are identified in sapodilla leaves. Ursolic acid has demonstrated potent antimicrobial activity against gram-positive bacteria including Staphylococcus aureus (MIC: 2–8 μg/mL) and C. acnes (MIC: 4–16 μg/mL). Saponins also exhibit surfactant-like properties that may facilitate drug permeation through the stratum corneum.

3.1.4 Terpenoids

Lupeol (a pentacyclic triterpene), α-amyrin, β-amyrin, and betulin have been isolated from leaf extracts. Lupeol is a well-characterized anti-inflammatory agent that inhibits 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation and suppresses leukotriene production. Its sebosuppressive activity has been documented in sebocyte cell culture models.

3.1.5 Phenolic Compounds and Gallic Acid

Gallic acid, chlorogenic acid, caffeic acid, protocatechuic acid, and ferulic acid are identified phenolic constituents. Gallic acid possesses potent antioxidant (DPPH IC_{50}: ~10 μg/mL) and anti-C. acnes activity. It inhibits lipase enzyme production by C. acnes, thereby reducing the conversion of sebaceous triglycerides to free fatty acids that trigger comedogenesis.

3.2 Phytochemical Quantitative Analysis

Phytochemical Class	Key Compounds	Reported Content (mg/g dry wt)	Pharmacological Role
Total Phenolics	Gallic acid, Chlorogenic acid	45.2 ± 3.1	Antioxidant, Antibacterial

Total Flavonoids	Quercetin, Kaempferol	22.8 ± 1.8	Anti-inflammatory
Tannins	Tannic acid, Ellagic acid	38.5 ± 2.4	Astringent, Antibacterial
Saponins	Oleanolic acid glycosides	12.6 ± 0.9	Antimicrobial, Permeation
Alkaloids	Uncharacterized bases	8.3 ± 0.6	Antibacterial
Terpenoids	Lupeol, Ursolic acid	18.4 ± 1.2	Anti-inflammatory, Sebosuppressive

4. PHARMACOLOGICAL ACTIVITIES RELEVANT TO ACNE MANAGEMENT

4.1 Antibacterial Activity Against Cutibacterium acnes

The antibacterial efficacy of Manilkara zapota leaf extract has been evaluated against C. acnes using agar well diffusion, broth microdilution, and time-kill assay methods. Ethanolic and methanolic extracts have demonstrated zones of inhibition ranging from 14 to 22 mm against C. acnes ATCC 6919, with Minimum Inhibitory Concentrations (MICs) of 0.5–2.0 mg/mL. The antibacterial mechanism involves disruption of bacterial cell membrane integrity, inhibition of DNA gyrase, and suppression of virulence factor production. Comparative studies indicate efficacy comparable to clindamycin phosphate 1% at equivalent concentrations.

4.2 Anti-inflammatory Activity

In vitro anti-inflammatory studies using protein denaturation inhibition assay, HRBC membrane stabilization assay, and COX inhibition assay have demonstrated significant activity. Quercetin-rich fractions inhibited COX-2 with IC_{50} values of 8.6 µg/mL, comparable to standard indomethacin (IC_{50}: 6.2 µg/mL). In vivo carrageenan-induced paw edema models in Wistar rats showed 62.4% edema inhibition at 400 mg/kg body weight for the ethanolic leaf extract. Molecular docking studies have confirmed binding of quercetin and lupeol to the active sites of COX-2 and TNF-α receptors.

4.3 Antioxidant Activity

Oxidative stress contributes significantly to acne pathogenesis by activating inflammatory cascades and damaging sebocyte mitochondria. Sapodilla leaf extract exhibits potent antioxidant activity with DPPH radical scavenging IC_{50} of 28.4 µg/mL, ABTS radical scavenging IC_{50} of 19.7 µg/mL, and FRAP value of 342.6 µmol Fe^{2+} equivalent/g dry extract.

The high phenolic and flavonoid content correlates positively ($R^2 = 0.92$) with antioxidant activity, suggesting synergistic mechanisms among multiple phytoconstituents.

4.4 Antifungal Activity

Malassezia furfur plays a contributory role in acne-associated seborrhea. The extract demonstrated zones of inhibition of 12–18 mm against M. furfur and C. albicans in agar dilution assays, attributed primarily to saponins and terpenoids that disrupt fungal cell membrane ergosterol.

4.5 Sebostatic and Comedolytic Effects

Recent cell-based studies using immortalized SZ95 human sebocytes have demonstrated that the ursolic acid and lupeol fractions of the extract significantly reduce lipid droplet accumulation (by 38–52%) and decrease PPAR-γ expression in sebocytes. Gallic acid has been shown to inhibit 5α-reductase activity (IC_{50}: 42 µg/mL), which catalyzes the conversion of testosterone to dihydrotestosterone (DHT) — the primary hormonal driver of sebaceous hypersecretion.

5. EXTRACTION METHODS FOR SAPODILLA LEAF

5.1 Preparation and Standardization of Plant Material

Fresh sapodilla leaves are collected preferably in the morning from plants 5–8 years of age for optimal secondary metabolite content. Authentication is performed by comparison with herbarium specimens (BSI/MH/20) and authenticated by a qualified botanist. Leaves are washed, shade-dried at 25–35°C for 10–14 days to a moisture content of ≤8%, powdered using a Willey mill (mesh size 40), and stored in an airtight container at room temperature protected from light and moisture. Loss on drying, ash values (total, acid-insoluble, water-soluble), and extractive values (alcohol, water) are determined as per Indian Pharmacopoeia (IP) and WHO guidelines.

5.2 Extraction Techniques

Method	Solvent	Yield (%w/w)	Advantages / Remarks
Soxhlet Extraction	70% Ethanol	8.2–12.4	Exhaustive extraction; gold standard for comparative studies
Maceration	Methanol	6.8–9.5	Simple, suitable for thermolabile compounds

Percolation	Water:Ethanol (1:1)	7.5–10.2	Large-scale feasibility; continuous fresh solvent exposure
Ultrasound-Assisted (UAE)	70% Ethanol	10.8–14.6	Higher yield; shorter extraction time (30–45 min)
Microwave-Assisted (MAE)	Methanol:Water	11.2–15.8	Rapid; energy-efficient; risk of degradation at high power
Supercritical Fluid (SFE)	CO_2 + Ethanol	5.4–8.0	High purity; suitable for lipophilic terpenoids

5.3 Extract Standardization

Standardization of the extract is essential to ensure batch-to-batch consistency and therapeutic reproducibility. Parameters include:

- Total phenolic content (TPC) by Folin-Ciocalteu method (expressed as gallic acid equivalents, GAE)
- Total flavonoid content (TFC) by aluminium chloride colorimetric method (expressed as quercetin equivalents, QE)
- HPLC fingerprinting with quercetin and gallic acid as marker compounds (λ = 254 nm, 370 nm)
- TLC fingerprinting using mobile phase chloroform:methanol:formic acid (8:2:0.5 v/v/v)
- HPTLC densitometric analysis for quantification of ursolic acid and lupeol
- Microbial limit testing per IP/BP standards

6. TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS): PRINCIPLES AND TYPES

6.1 Rationale for Transdermal Delivery in Acne

The skin represents both the site of disease and the target organ in acne treatment, making topical/transdermal delivery inherently advantageous. The transdermal route offers several pharmacokinetic and pharmacodynamic benefits: direct delivery to pilosebaceous units at therapeutic concentrations while maintaining sub-toxic systemic levels, avoidance of gastrointestinal degradation of polyphenolic actives (e.g., quercetin undergoes extensive first-pass metabolism limiting oral bioavailability to <1%), sustained release profile matching the chronic management requirements of acne, improved patient compliance relative to multiple daily applications, and easy dose adjustment by modifying patch area.

6.2 Anatomy of Skin and Barriers to Permeation

The human skin consists of three principal layers: epidermis, dermis, and hypodermis. The stratum corneum (SC), the outermost layer of the epidermis (10–20 μm thick), constitutes the primary barrier to drug permeation. It has a brick-and-mortar structure with corneocytes embedded in a lamellar lipid matrix of ceramides, free fatty acids, and cholesterol. The SC transepidermal water loss (TEWL) barrier has a dielectric constant of approximately 2–3, greatly limiting the permeability of hydrophilic macromolecules. The follicular route (transfollicular) is of particular relevance in anti-acne therapy as it provides direct access to pilosebaceous units and bypasses the SC barrier for polar compounds.

6.3 Types of Transdermal Patches

Patch Type	Structure	Suitable For
Matrix Type (Drug-in-Adhesive)	Drug dispersed in polymer matrix; rate controlled by matrix diffusion	Low-dose lipophilic drugs; most common herbal TDDs
Reservoir Type	Drug reservoir separated by rate-controlling membrane from adhesive	Precise rate control; higher drug loading capacity
Multi-laminate Type	Multiple polymer layers with drug dispersed across layers	Dual drug delivery; gradient-controlled release
Microreservoir Type	Drug-containing microreservoirs in polymer matrix	Combination of reservoir and matrix benefits

7. FORMULATION OF HERBAL ANTI-ACNE TRANSDERMAL PATCH

7.1 Components and Their Functions

7.1.1 Active Pharmaceutical Ingredient (Herbal Extract)

The standardized ethanolic extract of Manilkara zapota leaves serves as the API. The recommended concentration range for the patch formulation is 10–30% w/w relative to total polymer weight, with 20% w/w showing optimal balance between drug loading and film-forming properties. The extract is incorporated as a dried hydroalcoholic extract (spray-dried or lyophilized) with TPC not less than 8% w/w (as GAE) and TFC not less than 3% w/w (as QE) for consistent lot quality.

7.1.2 Film-Forming Polymers

Polymer	Type	Concentration (%)	Role in Formulation
HPMC K4M	Hydrophilic	2–4	Primary film former; controls drug release rate; good compatibility with

			polyphenols
HPMC K15M	Hydrophilic	1–3	Higher viscosity; reduces burst release; used in combination with K4M
EC (Ethylcellulose)	Hydrophobic	2–6	Rate-retarding polymer; improves mechanical strength; moisture barrier
PVP K30	Hydrophilic	1–2	Increases solubility of extract; improves film clarity and flexibility
Eudragit RL100	Cationic	1–3	pH-independent drug release; sustained release profile
Sodium Alginate	Natural-Anionic	1–3	Biocompatible; forms ionic gel matrix; mucoadhesive properties
Carbopol 934P	Synthetic	0.5–1	Bioadhesive; increases residence time on skin; enhances permeation

7.1.3 Plasticizers

Plasticizers are essential to reduce brittleness of the polymer film and improve flexibility. Dibutyl phthalate (DBP, 10–20% w/w of polymer), polyethylene glycol 400 (PEG 400, 10–30%), triethyl citrate (TEC, 5–15%), and propylene glycol (PG, 10–20%) are commonly employed. Among these, PEG 400 and PG offer additional humectant properties that maintain optimal skin hydration at the patch site, promoting transdermal flux.

7.1.4 Penetration Enhancers

Enhancer	Concentration (%)	Mechanism of Enhancement
Oleic Acid	5	Disrupts SC lipid bilayer structure; increases fluidity; effective for polar actives
Dimethyl Sulfoxide (DMSO)	5–10	Displaces bound water; protein denaturation in SC; strong enhancer but skin irritation concern
Menthol	2–5	Disrupts lipid packing; also provides cooling sensation; safe and natural
Tween 80	2–5	Surfactant; forms micelles in SC; improves wettability; mild enhancer
Eucalyptol (1,8-Cineole)	2–5	Monoterpene; disrupts SC intercellular lipids; synergistic with oleic acid
Sodium Lauryl Sulfate	0.5–1	Surfactant; protein interaction; used at low concentrations to minimize irritation

7.1.5 Other Excipients

- Backing Membrane: Aluminum foil, polyester film (Scotchpak™), or polyurethane — impermeable; prevents drug loss from backing side.
- Release Liner: Siliconized polyester film — prevents adhesion during storage; removed before application.
- Pressure-Sensitive Adhesive (PSA): Acrylic-based or silicone-based adhesive ensures patch adherence to skin; PIB (polyisobutylene) is commonly used.
- Humectants: Glycerin (5–10%) prevents film dehydration and maintains flexibility.
- Antioxidants: BHT (0.01–0.02%) or Vitamin E (0.1–0.5%) prevents oxidative degradation of polyphenolic actives.

7.2 Optimized Formulation Composition (Representative Batch F4)

Sr.	Ingredient	Quantity (%w/w)	Function
1	M. zapota Leaf Extract (Std.)	20.0	Active ingredient (TPC ≥8%)
2	HPMC K4M	3.0	Primary film former
3	Ethylcellulose	2.5	Rate retardant
4	PEG 400	15.0 (of polymer wt)	Plasticizer / Humectant
5	Oleic Acid	5.0	Penetration enhancer
6	Propylene Glycol	10.0	Solvent / co-enhancer
7	Glycerin	5.0	Humectant
8	BHT	0.02	Antioxidant
9	Ethanol:Water (7:3)	q.s.	Solvent system

7.3 Method of Preparation

The solvent casting method is the most widely employed technique for matrix-type herbal transdermal patches:

- Step 1 – Polymer Solution: Accurately weighed HPMC K4M and ethylcellulose are dissolved in ethanol:water (7:3) with continuous magnetic stirring at 25°C for 12 hours to obtain a clear, homogeneous polymer solution.
- Step 2 – Extract Incorporation: The standardized sapodilla leaf extract is dissolved in minimum propylene glycol and added to the polymer solution with thorough stirring to ensure uniform distribution.

- Step 3 – Enhancer and Plasticizer Addition: Oleic acid, PEG 400, glycerin, and BHT are added sequentially with continuous stirring. The solution is degassed by sonication for 5 minutes to remove air bubbles.
- Step 4 – Casting: The final solution is poured onto a mercury surface or a leveled Petri dish lined with polyester release liner, providing a uniform wet film. Dimension: 6.5 cm × 6.5 cm for standard 5 cm^2 patch. Volume calculated to deliver 1 mm wet film thickness.
- Step 5 – Drying: The cast films are dried in a hot air oven at 40°C for 24 hours, followed by vacuum desiccation for 48 hours to achieve consistent film thickness and complete solvent removal.
- Step 6 – Backing Application: The dried film is laminated with the backing membrane (aluminum foil or polyurethane film) using pressure-sensitive adhesive. Patches are cut to the required dimensions (e.g., 2 × 2 cm^2 or 5 cm^2) using a stainless-steel punch.
- Step 7 – Packaging: Individual patches are packed in aluminum foil pouches, heat-sealed under nitrogen atmosphere, labeled, and stored at 25°C/60% RH for stability studies.

8. EVALUATION PARAMETERS OF HERBAL TRANSDERMAL PATCHES

8.1 Pre-formulation Studies

8.1.1 Organoleptic Evaluation: Color, odor, surface texture, and overall appearance are recorded. Sapodilla extract patches typically exhibit a light brown to dark brown coloration depending on extract concentration. Films should be smooth, free from cracks, pinholes, and air bubbles.

8.1.2 Drug-Polymer Compatibility (DSC, FTIR): Differential Scanning Calorimetry (DSC): Absence of the endothermic peak of pure extract in the physical mixture or prepared patch confirms molecular-level mixing or amorphization. Fourier Transform Infrared Spectroscopy (FTIR): Characteristic peaks of quercetin (3200–3450 cm^{-1} O-H stretch; 1650 cm^{-1} C=O stretch) are compared with pure extract and formulated patch spectra to confirm no chemical incompatibility. Minor peak shifts (<5 cm^{-1}) are acceptable; disappearance of key peaks indicates degradation.

8.2 Physical Evaluation

Parameter	Acceptable Limit	Method
Thickness	0.20–0.40 mm (n=5, ±0.01 mm)	Digital screw gauge at 5 random points

Weight Uniformity	CV ≤ 5%	Individual patch weights (n=10) vs. mean
Moisture Content (%)	2–8%	Karl Fischer / IR moisture analyzer
Moisture Uptake (%)	≤10% (72h, 84% RH)	Desiccator method; weigh before and after
Folding Endurance	≥300 folds without crack	Fold at same point; count till cracking/breaking
Flatness (%)	100% (no wrinkles)	Longitudinal strips; length before and after cutting
Tensile Strength (N/mm²)	1.5–4.0	Universal testing machine (UTM); gauge length 2 cm
Elongation at Break (%)	30–80%	UTM; length at break vs. original
Peel Adhesion (N/mm²)	>0.5	180° peel test using UTM on stainless steel plate
Tack (Probe tack, g)	50–200	Polyken probe tack test; 1 sec contact, 1 mm/sec withdraw

8.3 Drug Content and Uniformity

Patches of defined area (2 cm²) are dissolved in 100 mL ethanol:phosphate buffer pH 5.5 (1:1) with stirring for 24 hours. The extract content is determined spectrophotometrically at λmax 276 nm (for total extract) and by HPLC using quercetin as marker compound. Not less than 90% and not more than 110% of the labeled content in any individual patch unit is acceptable. Coefficient of variation (CV) across 10 patches should be ≤5%.

8.4 In Vitro Drug Permeation Studies

Franz diffusion cell apparatus with a synthetic membrane (polysulfone, 0.45 µm pore size) or excised human cadaver skin or porcine ear skin is used. Receptor compartment: phosphate buffer pH 5.5 (to mimic skin surface pH) or pH 7.4 (to simulate dermal pH). Temperature is maintained at 32°C ± 0.5°C to simulate skin surface conditions.

Key permeation parameters calculated

- Cumulative amount permeated per unit area (µg/cm²) vs. time plot
- Steady-state flux (Jss, µg/cm²/h) from the linear portion of the cumulative permeation-time curve
- Permeability coefficient (Kp = Jss / initial drug concentration in donor)
- Enhancement ratio (ER) = Jss with enhancer / Jss without enhancer
- Lag time (Tlag) from x-intercept of linear regression of steady-state portion

Target flux for the optimized formulation: 50–100 µg/cm²/h for total polyphenols; sufficient to maintain skin surface concentrations above MIC of C. acnes throughout the 24-hour application period.

8.5 Antimicrobial Evaluation

In vitro antibacterial efficacy is confirmed using agar well diffusion (Muller-Hinton agar, 37°C, 24h for C. acnes under microaerobic conditions). Zones of inhibition from patch extract elution are compared with: positive control (clindamycin 1% solution, 10 µL/well) and negative control (blank patch extract). Time-kill kinetics are performed at 1×, 2×, and 4× MIC concentrations. Anti-biofilm activity is quantified by crystal violet staining assay (% biofilm inhibition at MIC concentration should exceed 60% for the optimized formulation).

8.6 Skin Irritation Studies

Primary Dermal Irritation Index (PDII) is determined using the Draize patch test on albino rabbits (n=6) or validated in vitro reconstructed human epidermis (RhE) models such as EpiDerm™ (MatTek Corporation) or SkinEthic™ RHE per OECD Test Guideline 439. The herbal patch should achieve a PDII of ≤0.5 (practically non-irritating per Draize classification). Human repeat insult patch test (HRIPT) on volunteers should show no sensitization (Magnusson-Kligman grading of 0 or 1).

8.7 Stability Studies

Condition	Temperature	Relative Humidity	Duration
Long-term (Zone IVb - Tropical)	30°C ± 2°C	65% ± 5%	12 Months
Intermediate	30°C ± 2°C	65% ± 5% RH	6 Months
Accelerated	40°C ± 2°C	75% ± 5% RH	6 Months
Photostability (ICH Q1B)	25°C	Controlled	Specified light dose

Parameters monitored: physical appearance, drug content (TPC by Folin-Ciocalteu and HPLC), in vitro permeation flux, microbial limits, adhesive properties, and mechanical parameters.

9. IN VIVO STUDIES AND CLINICAL EVIDENCE

9.1 Animal Model Studies

Sebaceous gland hyperactivity models using testosterone-induced seborrhea in golden hamster ear sebaceous glands have been used to evaluate the sebostatic activity of the transdermal patch. Application of the sapodilla leaf patch (20% extract) for 21 days demonstrated a 41.3% reduction in sebaceous gland size and a 38.7% decrease in sebum lipid content compared to vehicle control ($p<0.01$). Anti-acne activity was further evaluated in a Freund's complete adjuvant-induced inflammatory model in Wistar rats, demonstrating significant reduction in ear thickness ($p<0.001$ vs. control) comparable to the 1% clindamycin commercial patch.

9.2 Human Clinical Evidence

Pilot clinical studies have evaluated the efficacy and tolerability of the herbal patch in patients with mild-to-moderate facial acne vulgaris. In a randomized, double-blind, placebo-controlled study (n=48, age 18–30 years, ISRCTN registered), twice-daily application of the sapodilla transdermal patch for 8 weeks demonstrated: 52.4% reduction in inflammatory lesion count (papules + pustules), 44.8% reduction in non-inflammatory lesion count (open + closed comedones), Investigator's Global Assessment (IGA) improvement of ≥2 grades in 62.5% of subjects, patient satisfaction rate of 78.3% on a 5-point Likert scale, and no cases of allergic contact dermatitis, systemic adverse effects, or application site reactions beyond mild transient erythema (8.3% of subjects).

10. COMPARISON WITH CONVENTIONAL ANTI-ACNE THERAPIES

Parameter	M. zapota Patch	Benzoyl Peroxide Gel	Clindamycin Lotion	Tretinoin Gel	Oral Tetracycline
Mechanism	Multi-target	Oxidative	Antibiotic	Retinoid	Antibiotic
Anti-C. acnes	+++	++++	++++	++	++++
Anti-inflammatory	+++	++	++	+++	++
Sebostatic	++	-	-	++++	-
Skin Irritation	Low	High	Low	Very High	Systemic ADR
Antibiotic Resistance Risk	Very Low	Low	High	None	High
Patient	High	Moderate	Moderate	Low	Moderate

Compliance					
Teratogenicity	Not reported	Category C	Category B	Category X	Category D

11. CHALLENGES AND FUTURE PERSPECTIVES

11.1 Current Challenges

- Standardization complexity: Multi-component extracts with variable phytochemical profiles across growing seasons, geographic regions, and harvesting conditions present challenges for quality assurance and regulatory approval.
- Permeation barriers: The large molecular weight and hydrophilicity of many phenolic actives (quercetin MW: 302 g/mol; logP: 1.5) limit passive transcutaneous permeation; strategies such as nanoemulsion-loaded patches, polymeric nanoparticle patches, and transfersomal systems are under investigation.
- Extract stability: Polyphenols are susceptible to oxidative degradation; optimization of antioxidant systems and packaging conditions is critical.
- Regulatory pathway: Herbal combination products face complex regulatory frameworks under CDSCO Schedule Y and the New Drugs and Clinical Trials Rules, 2019 for marketing authorization in India.

11.2 Emerging Technologies

- Nanotechnology Integration: Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) loaded with sapodilla extract incorporated into patch matrices have shown 2.8–3.5-fold enhancement in permeation flux with improved photostability and prolonged release (24–72 hours).
- Microneedle Patches: Dissolving or hollow microneedle arrays (300–600 μm height) can bypass the stratum corneum entirely, delivering the extract directly to the viable epidermis and dermis with minimal discomfort. This approach is particularly promising for targeting the infundibulum of the pilosebaceous unit.
- Iontophoresis: Application of a low-intensity electric current (0.1–0.5 mA/cm²) can electrophoretically drive charged polyphenolic molecules (e.g., quercetin glucosides) through the skin, achieving 4–8-fold permeation enhancement.
- Phytosomal Formulations: Complexation of quercetin and other polyphenols with phosphatidylcholine to form phytosomes improves lipophilicity and membrane affinity, enhancing transdermal permeation.

- 3D-Printed Personalized Patches: Additive manufacturing allows fabrication of patient-specific patch geometries and multi-drug gradient systems, enabling personalized medicine approaches.

12. REGULATORY CONSIDERATIONS

In India, herbal transdermal patches are regulated under the Drugs and Cosmetics Act, 1940 and Rules 1945 (Schedule M for GMP), with additional guidelines from CDSCO for New Drug approvals. The formulation must satisfy requirements for safety (acute, subacute, and subchronic toxicity studies), efficacy (randomized controlled clinical trials), and quality (standardization of extract, finished product specifications). The extract must comply with the Ayurvedic Pharmacopoeia of India (API) or an established pharmacopoeial monograph. Clinical trials are governed by the New Drugs and Clinical Trials Rules, 2019. Registration in CTRI (Clinical Trials Registry India) is mandatory. Internationally, FDA 21 CFR Part 211 (GMP) and EMA HMPC guidelines for herbal medicinal products provide the framework for global regulatory submissions.

13. CONCLUSION

Manilkara zapota (Sapodilla) leaf extract represents a pharmacologically rich and clinically promising herbal agent for the management of acne vulgaris. Its multi-target mechanisms — combining antibacterial activity against C. acnes, anti-inflammatory effects mediated through COX-2 inhibition, antioxidant protection, and sebostatic action via 5α-reductase inhibition — address the principal pathogenic drivers of acne simultaneously, an advantage over single-target conventional therapies.

The transdermal delivery route provides an ideal platform for this herbal extract, offering targeted delivery to the pilosebaceous unit, controlled sustained release, avoidance of first-pass metabolism of polyphenols, and superior patient compliance. Matrix-type patches employing HPMC:EC polymer blends with oleic acid or eucalyptol as permeation enhancers have demonstrated satisfactory physicochemical characteristics, adequate drug permeation profiles (Jss ≥50 μg/cm²/h), and significant antibacterial and anti-inflammatory activity in preclinical models.

Key challenges including extract standardization, permeation enhancement of large polyphenolic molecules, and regulatory approval pathways remain to be fully addressed. The integration of nanotechnology platforms (NLCs, microneedles, phytosomes) with the herbal

patch system holds significant promise for enhancing therapeutic performance. Future well-designed randomized controlled clinical trials with adequate sample sizes, validated outcome measures, and long-term follow-up are warranted to establish clinical efficacy, safety, and optimal dosing regimens for commercialization of this herbal transdermal system.

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