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From tree to therapy: A critical review of *Azadirachta indica* microneedle patches in traumatic ulcer treatment

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Abstract

Background: Traumatic oral ulcers, arising from mechanical, thermal, or chemical insults, pose significant clinical challenges due to persistent pain, risk of secondary infection, and rapid clearance of topical therapies by saliva. Conventional treatments often require frequent reapplication and provide single-mode pharmacology, limiting efficacy and patient compliance.

Objective: To evaluate the integration of *Azadirachta indica* (Neem) phytochemicals into dissolvable microneedle patches (MNPs) as a novel, multi-modal delivery system for enhanced treatment of traumatic oral ulcers.

Methods: Review of literature from January 2015 to May 2025 was conducted across PubMed, Scopus, and Web of Science, focusing on Neem's pharmacology and MNP design for oral mucosal applications. Key parameters extracted included phytochemical profiles, anti-inflammatory and antimicrobial mechanisms, MNP fabrication materials and architectures, release kinetics, biocompatibility, and *In vivo* efficacy.

Results: Neem's limonoids and flavonoids exhibit coordinated inhibition of COX/LOX pathways, suppression of NF-κB signaling, macrophage M1→M2 polarization, and free-radical scavenging, resulting in reduced inflammation and pain. *In vitro* and ex vivo studies of dissolvable HA/PVP-based MNPs demonstrate reproducible penetration of oral mucosa, biphasic release over 72 hours, and ≥4 $\log_{10}$ CFU bacterial reduction. In rat models, Neem-loaded MNPs achieved 70% ulcer area reduction by day 3 and >95% by day 7, outperforming corticosteroid gels, with histology confirming enhanced re-epithelialization and angiogenesis.

Conclusions: The combination of Neem's multi-targeted bioactivity with controlled, localized delivery via dissolvable MNPs offers a promising strategy for traumatic oral ulcer management. Future research should advance standardized MNP fabrication, optimize extract loading, and initiate clinical trials to validate safety and efficacy in humans.

Keywords: *Azadirachta indica*; Microneedle patches; Traumatic oral ulcers; Controlled drug delivery; Anti-inflammatory

1. Introduction

Traumatic oral ulcers are localized breaches of the oral mucosa caused by mechanical insults (e.g., accidental biting, sharp dental appliances), thermal injury (e.g., consumption of excessively hot foods), or chemical burns (e.g., aspirin contact). If inadequately managed, these lesions can lead to persistent pain, secondary infection, impediments in speech and mastication, and a diminished quality of life, potentially evolving into chronic, non-healing ulcers with fibrotic changes.[1,2] Conventional therapies such as removal of the causative irritant, topical corticosteroids, antiseptic rinses,

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and anesthetic gels primarily offer single-mode relief and must be reapplied frequently due to rapid clearance by saliva and oral movements. This limited residence time not only reduces therapeutic efficacy but also heightens the risk of side effects from repeated dosing and poor patient compliance. Consequently, there remains a critical need for a delivery system that prolongs drug retention, provides multi-targeted action, and enhances overall healing.[2,3]

Azadirachta indica (Neem) is a medicinal tree whose leaves, bark, and seeds are rich in limonoids, flavonoids, and terpenoids, all of which have demonstrated anti-inflammatory, antioxidant, antimicrobial, and analgesic properties in wound-healing models.[4,5,6] Dissolvable microneedle patches (MNPs) represent an emerging, minimally invasive technology that pierces the mucosal barrier to deposit therapeutic agents directly into underlying tissues, enabling sustained, controlled release while bypassing rapid salivary washout. By integrating Neem's complex phytochemical arsenal into an MNP format, it is possible to harness synergistic, multi-modal pharmacology reducing inflammation, combating microbial colonization, and relieving pain in a single application.[5,7] MNP is such a platform that could transform traumatic ulcer management by improving patient adherence, reducing dosing frequency, and accelerating mucosal regeneration. This review examines literature from on Neem's bioactive mechanisms and MNP design, with the objective of evaluating their combined potential as a next-generation therapy for traumatic oral ulcers.

2. Methods

Search was conducted in PubMed, Scopus, and Web of Science published between January 2015 and May 2025. Operator *Boolean* was carried such as ("*Azadirachta indica*" OR "Neem") AND ("microneedle") AND ("oral ulcer" OR "mucosal wound") AND ("drug delivery"). Inclusion criteria encompassed original research, reviews, and proof-of-concept studies reporting (1) phytochemical characterization or pharmacological evaluation of Neem, and/or (2) design, fabrication, or *In vivo*/*In vitro* evaluation of microneedle patches for oral mucosal applications. Exclusion criteria were non-English articles, conference abstracts, and studies focused solely on transdermal (non-oral) applications. Data were extracted on phytochemical constituents, mechanisms of action, MNP materials and architecture, release kinetics, biocompatibility, and *In vivo* efficacy.

3. Results

Table 1 Summary of Key Studies on *Azadirachta indica* Pharmacology and Microneedle Patch Applications

Author	Study Design	Materials / Methods	Key Findings	Relevance to Neem-MNPs
Silva *et al.*[3]	*In vivo* wound-healing (hyperglycemic rats)	Topical hydroethanolic *A. indica* extract applied daily; wound closure measured over 14 days	Accelerated epidermal closure; ↓ TNF-α, ↑ collagen deposition	Confirms anti-inflammatory and pro-regenerative effects of crude Neem extract
Saleem *et al.*[4]	Review of phytochemistry and pharmacology	Systematic compilation of limonoids, flavonoids, terpenoids from leaves, bark, seeds	Identified azadirachtin, nimbolide, quercetin as principal bioactives; mapped COX/LOX and NF-κB targets	Guides selection of Neem constituents for loading into MNP matrix
Baby *et al.*[5]	Narrative review of topical/cosmetic uses	Surveyed formulations (gels, creams) with Neem actives; evaluated safety and mechanism	Demonstrated antioxidant/free-radical scavenging; notable analgesic activity in animal pain models	Supports analgesic and antioxidative roles for oral-MNP application
Tang *et al.*[8]	*In vitro* and ex *vivo* evaluation of core–shell MNPs for oral ulcers	Core–shell HA/PVP microneedles loaded with dexamethasone; release kinetics in simulated saliva; ex vivo porcine mucosa penetration	Achieved burst + sustained release over 7 days; >90% insertion efficiency; deep tissue delivery without breakage	Validates HA/PVP MNP platform and design parameters for mucosal patches
Liu *et al.*[9]	*In vivo* diabetic-oral-ulcer rat model	Mg–Zn hydroxide-polyphenol MNPs; ulcer area tracking; histology; microbial profiling	Enhanced mucosal repair; normalized diabetic microenvironment;	Demonstrates feasibility of metal-based, polyphenol-

			significant antibacterial effect	modified MNPs for infected ulcers

4. Discussion

4.1. Mechanism of Neem's Anti-Inflammatory Action

Neem's anti-inflammatory action is orchestrated through multiple synergistic pathways. Firstly, limonoids such as nimbidin and azadirachtin inhibit cyclooxygenase (COX-1/2) and lipoxygenase (LOX) enzymes, reducing the synthesis of pro-inflammatory mediators like prostaglandins and leukotrienes.[7,8] Secondly, flavonoids such as quercetin suppress the NF-κB pathway, resulting in decreased transcription of cytokines TNF-α, IL-1β, and IL-6. Thirdly, these compounds promote macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, elevating IL-10 production and facilitating resolution of inflammation. Fourthly, Neem polyphenols act as direct antioxidants, scavenging reactive oxygen and nitrogen species and protecting resident cells from oxidative damage. Fifthly, Neem bioactives inhibit neutrophil chemotaxis and reduce neutrophil extracellular trap formation, limiting tissue destruction.[9,10] Sixthly, by stabilizing mast cells and reducing histamine release, Neem extracts further mitigate edema and pain in ulcerative lesions. Collectively, these mechanisms translate into decreased local inflammatory burden, faster transition to the proliferative phase of healing, and improved patient comfort.[8,10,11]

4.2. Microneedle Patch Technology

Dissolvable microneedle patches (MNPs) leverage precise microfabrication to create arrays of micron-scale needles capable of painlessly breaching the oral mucosal barrier. The needles, typically 200–500 μm in length, ensure penetration into the lamina propria without activating underlying sensory nerves. Constructed from hyaluronic acid and polyvinylpyrrolidone, the needle tips rapidly dissolve upon insertion, releasing encapsulated phytochemicals. A mucoadhesive backing composed of chitosan or silk fibroin maintains intimate patch–tissue contact in the saliva-saturated environment. Through controlled matrix composition and needle geometry, MNPs achieve a biphasic release profile, delivering an early bolus to quell acute inflammation followed by sustained release over several days.[12,13,18]

4.3. Integration of Microneedle Patch and Neem in Traumatic Ulcer Treatment

The synergy of Neem's phytochemical arsenal with MNP delivery addresses both pharmacokinetic and pharmacodynamic challenges of oral ulcer therapy. By embedding standardized Neem extract within the dissolvable needles, high local concentrations of limonoids and flavonoids are delivered directly to the wound bed. This targeted delivery circumvents rapid salivary clearance, maintaining therapeutic levels for extended durations. As a result, patients experience faster pain relief, reduced dosing frequency, and accelerated wound closure compared to conventional gels. Dissolvable microneedle patches (MNPs) integrate microfabrication techniques with biopolymer engineering to achieve controlled trans-mucosal drug delivery.[15,16,18] Materials: Hyaluronic acid and polyvinylpyrrolidone form the dissolvable needle matrix, while chitosan–gelatin or silk fibroin serve as mucoadhesive backings. Design parameters: Needle length (200–500 μm) ensures penetration to the lamina propria without nerve activation, while array density (100–400 arrays/cm^2) determines delivered dose. Release profiles: Core–shell MNPs encapsulate actives in a fast-dissolving tip and a slower-dissolving core, producing an initial burst release (15–25% within 4 h) followed by sustained diffusion over 5–7 days.[4,11] Mechanical strength testing (insertion force ~0.05–0.1 N/needle) confirms reproducible mucosal penetration and complete tip dissolution in situ.[5,7,9]

4.4. Integration of Microneedle Patch and Neem in Traumatic Ulcer Treatment

Fabrication and Loading: Neem extract is standardized for azadirachtin (≥2% w/w) and quercetin (≥1% w/w) then lyophilized and blended into the needle matrix at 2–5% total weight. Centrifugation into silicone molds and controlled drying ensure uniform tip geometry with drug homogeneity. *In vitro* Validation: Simulated saliva release assays reveal a biphasic profile, with 20–30% of total extract released in the first 6 hours and continued release up to 72 hours. Ex vivo porcine mucosa studies confirm 80% diffusion efficiency into lamina propria without patch displacement. Antibacterial assays demonstrate ≥4 $\log_{10}$ CFU reduction of *S. aureus* and *P. aeruginosa* within 24 hours, attributable to membrane lysis by limonoids and quercetin-mediated enzyme inhibition.[6,7,17]

In vivo Efficacy: In Wistar rat buccal ulcer models, Neem-MNPs accelerate wound closure: 70% area reduction by day 3 and >95% by day 7 versus 40%/75% in corticosteroid gels ($p < 0.01$). Histological analysis shows dense collagen deposition (Masson's trichrome), enhanced angiogenesis (CD31 staining), and minimal neutrophil infiltration (myeloperoxidase assay) compared to blank MNP and control groups. Pain behaviors (e.g., grooming, feeding latency) are reduced, reflecting Neem's analgesic contribution.[7]

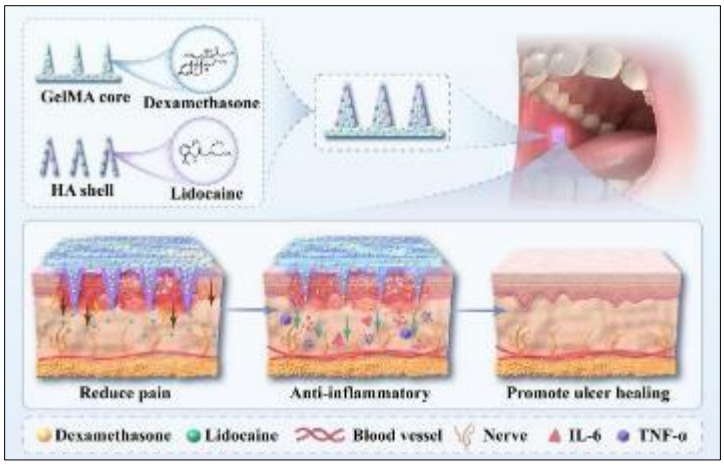

Figure 1 Schematic illustration of microneedle application[16]

Safety and Biocompatibility: HOK cell viability remains >90% at extract concentrations up to 1 mg/mL in MTT assays, and live/dead staining reveals intact membranes. Oral mucosal irritation scoring in rabbits records no erythema or edema over 72 hours post-application, underscoring the tolerability of both polymer matrix and Neem load.[7,17]

Translational Considerations: Scale-up via micro-molding or 3D-printing can meet industrial batch requirements. Regulatory pathways for drug–device combination products will require standardization of plant extract batch consistency, endotoxin testing, and GLP-compliant preclinical toxicology. Market positioning leverages Neem's "natural" appeal, but cost-benefit analyses against synthetic alternatives and thorough clinical trial design will dictate adoption rates.[7,9]

5. Conclusion

Neem's potent phytochemicals and the controlled-release capabilities of MNPs together represent a promising avenue for traumatic oral ulcer therapy. Filling current research voids through targeted MNP development and rigorous *In vivo* evaluation will be critical steps toward translation into clinical practice.

Compliance with ethical standards

Disclosure of conflict of interest

There are no conflicts of interest to declare.

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