The potential of oral microneedle patches as a delivery system for golden sea cucumber collagen and snakehead fish albumin for oral mucosal wound healing

Potensi oral *microneedle patch* sebagai sistem penghantaran kolagen teripang emas dan albumin ikan gabus untuk penyembuhan luka mukosa mulut

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ABSTRACT
This review analyses the potential for synergistic integration between golden sea cucumber (*Stichopus hermanni*) collagen and snakehead fish (*Channa striata*) albumin via a mucoadhesive oral microneedle patch delivery system to accelerate wound healing. This study employs a comprehensive literature review, exploring the biology of mucosal wound healing, the biochemical profiles of the golden sea cucumber and snakehead fish components, and the mechanism of microneedle technology. Type I collagen from the golden sea cucumber acts as a structural scaffold and a provider of proliferative signals through its interaction with integrins. Meanwhile, catfish albumin functions as an anti-inflammatory agent, an osmotic pressure balancer, and a provider of essential metabolic nutrients (such as zinc and amino acids) that support the proliferation phase. The use of dissolving microneedle technology enables precise, pain-free penetration through the epithelial barrier, whilst delivering the effects of percutaneous collagen induction therapy via mechanical microtrauma that stimulates the healing cascade. The design of a double-layered hybrid patch with a mucoadhesive layer has been shown to maintain drug retention in the moist oral cavity environment. The integration of *S.hermanni* collagen and *C.striata* albumin into the oral microneedle system promises a revolutionary therapeutic approach to the management of mucosal wounds through the simultaneous modulation of the NF-κB and TGF-β1 signalling pathways.
Keywords: *Channa striata,* microneedle patch, oral mucosa, *Stichopus hermanni,* wound healing

ABSTRAK
Tinjauan ini menganalisis potensi integrasi sinergis antara kolagen teripang emas (*Stichopus hermanni*) dan albumin ikan gabus (*Channa striata*) melalui sistem penghantar berupa *oral microneedle patch* mukoadesif untuk mempercepat penyembuhan luka. Penelitian ini menggunakan metode kajian pustaka komprehensif dengan mengeksplorasi biologi penyembuhan luka mukosa, profil biokimia komponen teripang emas dan ikan gabus, serta mekanisme teknologi *microneedle*. Kolagen tipe I dari teripang emas berperan sebagai *structural scaffold* dan penyedia sinyal proliferatif melalui interaksi dengan integrin. Sementara itu, albumin ikan gabus berfungsi sebagai agen anti-inflamasi, penyeimbang tekanan osmotik, serta penyedia nutrisi metabolik esensial (seperti seng dan asam amino) yang mendukung fase proliferasi. Penggunaan teknologi *dissolving microneedle* memungkinkan penetrasi yang presisi dan tanpa rasa nyeri melalui barier epitel, sekaligus memberikan efek *percutaneous collagen induction therapy* (PCIT) melalui trauma mikro mekanis yang menstimulasi kaskade penyembuhan. Desain *patch* hibrida berlapis ganda dengan lapisan mukoadesif terbukti mampu mempertahankan retensi obat dalam lingkungan rongga mulut yang lembab. Integrasi kolagen *S.hermanni* dan albumin *C.striata* ke dalam sistem *microneedle oral* menjanjikan suatu pendekatan terapeutik yang revolusioner untuk penatalaksanaan luka mukosa melalui modulasi simultan jalur pensinyalan NF-κB dan TGF-β1.
Kata kunci: *Channa striata, microneedle patch,* mukosa oral, *Stichopus hermanni,* penyembuhan luka
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INTRODUCTION

The oral cavity is a highly unique and dynamic anatomical environment that is constantly exposed to various mechanical, thermal, and chemical stresses, as well as pathogenic microorganisms.[1] These conditions make the oral mucosa highly susceptible to various forms of trauma that can lead to lesions, traumatic ulcers, and chronic inflammatory conditions such as aphthous stomatitis and oral submucosal fibrosis.[1,2] The incidence of oral mucosal disorders continues to rise globally and significantly reduces patients' quality of life through clinical manifestations such as acute pain, masticatory difficulties, dysphagia, and speech difficulties.[1] Historically, conventional therapy for healing oral mucosal wounds has relied heavily on the application of topical pharmacological agents such as gels, ointments, creams, or analgesic and corticosteroid mouthwashes.[3] However, this route of oral topical administration faces significant biological and physiological barriers. The wash-out effect caused by constant saliva flow, mechanical movement from masticatory and phonatory, and enzymatic degradation by salivary proteases contribute to a very short drug retention time at the wound site, ultimately resulting in suboptimal therapeutic bioavailability.[1,3]

In an effort to address these limitations, the past decade has witnessed a massive paradigm shift toward tissue engineering-based interventions and the use of natural biomaterials for the management of both acute and chronic wound healing.[4] The exploration of natural resources, particularly from marine and freshwater biodiversity, has paved the way for identification of highly potent regenerative agents. Marine collagen extracted from the golden sea cucumber (*S.hermanni*) and albumin protein isolated from the snakehead fish (*C.striata*) have garnered significant attention among biomedical researchers.[4]

These two biological macromolecules demonstrate promising therapeutic efficacy; golden sea cucumber collagen provides a structural scaffold and proliferative signals, while snakehead fish albumin supplies essential metabolic nutrients and acts as a potent anti-inflammatory agent and osmotic balancer.[5,6] Although the bioactive profiles of these two agents are truly impressive, the primary pharmacokinetic challenge remains focused on how to deliver these large molecules through the damaged mucosal epithelial barrier so they can reach the lamina propria, where the actual tissue repair process occurs.[3,7]

As a revolutionary solution to these delivery limitations, oral microneedle technology has been proposed as the transmucosal delivery system of the future. This technology utilizes an array of micrometer-scale needles that enable precise penetration into the mucosal epithelium without stimulating pain receptors (e.g., nociceptors) in deeper tissues.[1,2] Microneedles bypass the physical barriers of the tissue and deliver therapeutic macromolecules directly into the local microcirculation.[3] This literature review presents an extensive and analytical overview of the potential for synergistic integration of golden sea cucumber collagen and snakehead fish albumin into an oral mucoadhesive microneedle patch system. Therefore, this review was conducted to synthesize current evidence regarding oral microneedle technology and its potential integration with golden sea cucumber collagen and snakehead fish albumin as a novel regenerative strategy for enhancing oral mucosal wound healing.

LITERATURE STUDIES

The biology of oral mucosal wound healing

Wound healing is a fundamental biological defense mechanism and a complex process of homeostasis maintenance, dedicated to

restoring tissue integrity following anatomical trauma.[1,8] Although it shares basic principles with skin wound healing, the biology of oral mucosal wound healing exhibits an intrinsically different and far superior regenerative phenotype.[2] This phenotype is characterized by a significantly faster asymptotic rate of wound closure and a minimal tendency toward scar formation; in fact, healing often occurs via *restitutio ad integrum* that is, a return to the original state without structural defects.[1,2] Understanding the biological architecture and cellular dynamics of this process is crucial for designing drug delivery systems that can seamlessly interact with the oral wound microenvironment.

The healing process of the oral mucosa is a dynamic cascade involving closely coordinated spatial and temporal interactions among various cell populations, the extracellular matrix, and signaling molecules.[3,9] This cascade is classically divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling.[1,3] The first phase, hemostasis, is initiated within seconds to minutes immediately after vascular integrity is compromised. The injury triggers a local neurogenic reflex and the release of potent vasoactive mediators, such as endothelin-1, which induce transient vasoconstriction to minimize blood loss.[2] Furthermore, circulating platelets adhere to the damaged vascular surface, undergo activation, and aggregate to form a primary hemostatic plug. At the same time, activation of the coagulation cascade results in thrombin generation, which catalyzes the conversion of soluble fibrinogen into insoluble fibrin fibers. The resulting fibrin network stabilizes the platelet plug, forming a blood clot that not only prevents further blood loss but also serves as a temporary extracellular matrix that supports the migration, recruitment, and proliferation of cells essential for tissue repair and regeneration.[10]

Within the oral cavity, this fibrin clot not only functions as a physical seal that stops bleeding but also provides a provisional matrix that is crucial for facilitating the migration of immune cells and fibroblasts in the following hours.[1] Furthermore, the release of Damage-Associated Molecular Patterns (DAMPs) from necrotic cells sends chemotactic signals that initiate the inflammatory phase.

During the inflammatory phase, which lasts from several hours to several days after injury, polymorphonuclear leukocytes (primarily neutrophils) migrate to the wound site under the influence of chemokines such as CXCL8 and perform biological debridement through phagocytosis of pathogens and release of proteolytic enzymes.[1] Subsequently, circulating monocytes infiltrate the wound and differentiate into macrophages, which phagocytose apoptotic neutrophils and secrete cytokines and growth factors that initiate the proliferative phase. Oral wound healing is characterized by a significantly attenuated inflammatory response compared with skin, with lower expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and interleukin-1β (IL-1β).[2,3] This rapid resolution is facilitated by salivary bioactive molecules, including histatin, epidermal growth factor (EGF), and antimicrobial peptides, which suppress excessive inflammation and protect against the microbial invasion.[3] The proliferative phase is characterized by angiogenesis, re-epithelialization, and granulation tissue formation. Keratinocytes at the wound margins undergo phenotypic changes and migrate across the provisional matrix to close the defect. Oral mucosal cells exhibit a *primed state*, with constitutive upregulation of *epidermal growth factor receptor* (EGFR) and cell-cycle-associated genes, contributing to rapid re-epithelialization.[2,4] Simultaneously, fibroblasts synthesize type III collagen, hyaluronic acid, and fibronectin to form granulation tissue, while *vascular endothelial growth factor* (VEGF) promotes neovascularization to restore oxygen and nutrient supply.[1] The remodeling phase, which may persist for weeks to months, involves the replacement of type III collagen with thicker type I collagen through *matrix metalloproteinase* (MMP)-mediated remodeling.[1,5] Fibroblast differentiation into α-smooth muscle actin (α-SMA)-expressing myofibroblasts mediates wound contraction. In oral mucosa, myofibroblast activity and tissue contraction occur more rapidly and terminate earlier than in skin, resulting in reduced fibrosis and improved functional recovery.[3,5]

A deep understanding of these biological stages underscores that any exogenous therapeutic intervention, such as a microneedle patch, must be designed not only to withstand the wet and enzymatically aggressive saliva environment, but also to resonate with the intrinsic cell proliferation rate of the mucosa. The delivery system must be capable of stimulating the proliferation phase earlier without prolonging the inflammatory phase, ensuring a smooth transition toward scar-free remodeling.

Role of the extracellular matrix and collagen in wound healing

The ECM is a dynamic and bioactive network of proteins and glycans that provides structural support to cells while actively regulating cellular behavior and playing a crucial role in all stages of soft tissue repair.[11] Following tissue injury, ECM degradation recruits fibroblasts to form a temporary matrix, while ECM-derived biopolymers such as collagen, hyaluronic acid, fibrin, and gelatin can be crosslinked to create scaffolds that support cell infiltration and tissue repair.[12] As healing progresses, this provisional matrix is replaced by a stronger fibrous protein network, primarily collagen. Maintaining a carefully calibrated balance between ECM synthesis and enzymatic degradation by MMPs is critical, as excessive matrix stiffness can trigger uncontrolled myofibroblast activity, leading to severe fibrotic scarring.[13] Collagen, accounting for 50-90% of the ECM's protein composition, plays a biological role that far exceeds mere structural support.[14] Immediately upon injury, exposed subendothelial collagen triggers platelet activation and the secondary coagulation cascade to form a hemostatic plug.[15] Entering the inflammatory phase, collagen exhibits surprising immunomodulatory functions; its degraded peptide fragments act as chemotactic guides for immune cells.[11] Furthermore, collagen-based scaffolds have been reported to promote macrophage polarization from the pro-inflammatory M1 phenotype toward the reparative M2 phenotype, contributing to improved tissue regeneration.[16] ECM components such as fibronectin, collagen, and glycosaminoglycans support angiogenesis by providing a structural framework and regulating endothelial cell signaling for new blood vessel formation.[17] Because of its unparalleled biocompatibility and intrinsic bioactivity, the use of exogenous collagen such as matrices and hydrogels has become the gold standard in reconstructive surgery.[18] Providing this exogenous collagen substrate not only fills structural deficits but also actively drives cellular signal transduction, accelerating tissue repair at a speed and quality that surpasses the body's natural regenerative capabilities.[18]

Bioactive compounds of *S.hermanni*

The golden sea cucumber is a potent marine regenerative agent with a long history in traditional medicine for treating inflammation and accelerating wound healing.[1] Modern biochemical evaluations reveal that its body wall contains an extraordinarily complex and bioactive molecular matrix, which includes structural polysaccharides like glycosaminoglycans (GAGs) and chondroitin sulfate, secondary meta-

bolites, antioxidant phenols, and essential polyunsaturated fatty acids (PUFAs), notably EPA and (6Z)-octadecenoic acid.[21,22]

For tissue engineering, the most pharmacologically valuable macromolecule extracted from this marine organism is type I marine collagen.[20] Extraction studies confirm that this collagen fully retains its triple-helix hydrogen-bond formation, which is vital for fibroblast functionality, and is rich in structural amino acids like glycine, proline, and hydroxyproline.[20] Crucially, marine collagen serves as a highly sought-after, universal biomaterial because it eliminates the risk of zoonotic pathogen transmission and bypasses the socio-cultural and religious restrictions associated with mammalian collagen sourcesi.[20,23]

In vivo experiments demonstrate that these extracts comprehensively accelerate tissue closure by downregulating NF-κB to suppress aggressive inflammation, while concurrently activating the Nrf2 pathway to protect fibroblasts from oxidative stress.[21,22] Furthermore, in models of traumatic oral ulcers, topical application of an 80% water extract remarkably accelerated healing by upregulating local type I collagen expression and stimulating neovascularization via VEGF.[19] This rapid structural recovery is further enhanced by the presence of GAGs and chondroitin sulfate, which synergistically promote collagen cross-linking for a robust granulation matrix.[19]

The role of albumin in tissue repair

Albumin is a 66 kDa protein exclusively synthesized by hepatocytes and is the most abundant plasma protein, accounting for approximately 50% of total plasma protein content.[24] While historically defined merely as a homeostatic regulator responsible for maintaining vascular colloid osmotic pressure to prevent massive fluid extravasation, modern pathophysiology recognizes it as a highly versatile, multi-tasking protein. In the context of tissue repair, albumin carries out vital functions to maintain cellular survival, neutralize tissue toxicity, and actively facilitate the biological architecture of wound healing.[25]

Pharmacokinetically, albumin serves as the principal plasma carrier protein, employing distinct binding domains to transport a wide range of endogenous and exogenous molecules, including free unsaturated fatty acids, steroid hormones, inorganic ions, and essential micronutrients.[26] This transport capability is critical during the late inflammatory and early proliferation phases of wound healing, when the local demand for metabolic energy and structural precursors skyrockets. By ensuring adequate perfusion directly into the wound bed, albumin guarantees that the supply of these amino acids and fatty acids proceeds without disruption to support dividing keratinocytes and matrix-synthesizing fibroblasts.[26]

Beyond molecular distribution, albumin acts as a potent frontline extracellular antioxidant; its highly reactive cysteine-34 residue directly binds and neutralizes toxic reactive oxygen species (ROS) released during the neutrophil respiratory burst. Furthermore, it coordinates essential transition metals like zinc and copper, boosting local superoxide dismutase (SOD) activity to radically suppress lipid peroxidation and inhibit the proteolytic degradation of the ECM.[26] Clinically, correcting albumin deficits normalizes both intravascular and topical levels, which subsequently modulates NF-κB signaling, suppresses fibroblast apoptosis, and accelerates recovery from the stagnant inflammation responsible for non-healing chronic wounds.[25,26]

Therapeutic potential of snakehead fish albumin

The snakehead fish (*C.striata*) is an endemic Southeast Asian freshwater species with a robust history in traditional medicine for post-surgical and burn recovery.[22] Modern analysis confirms it as a superior non-mammalian reservoir for albumin, exhibiting an extraordinary total protein fraction of up to 44.9% and pure, glycogen-free sarcoplasmic albumin concentrations reaching 13.44% under specific environmental conditions.[22,23,27] Alongside this highly pure albumin, the biological system of *C.striata* contains other healing agents like striatin, high zinc levels, and essential Omega-3 and Omega-6 fatty acids, which collaborate with helical amino acids (glycine, alanine) to act as absolute raw materials for new collagen fiber synthesis.[23,26,27]

Clinical and *in vivo* trials, including dental models for dry socket complications, demonstrate its comprehensive capabilities by significantly normalizing the bone socket repair process and preventing blood clot failure.[28] Molecularly, this concentrated extract works by stimulating recruited functional platelets and neutrophils to secrete significantly higher quantitative intensities of Transforming Growth Factor-beta 1 (TGF-β1).[26,28] This high-level regulation of TGF-β1 acts as a crucial transcription inducer, compelling neighboring keratinocytes and lamina propria fibroblasts into a massive proliferative cycle that drastically shortens the time required for wound defect contraction.

Further histological insights reveal the specific ability of *C.striata* albumin to modulate microcapillary remodeling and effectively repolarize inflammatory immune cells.[26] High concentrations of pure albumin extract effectively suppress pro-inflammatory macrophages and exponentially decrease ectopic neovascularization density in the late inflammatory phase, ensuring a smooth regenerative transition to a dense, mature epithelial layer without prolonged exudation. Combined with its anti-edematous, microbicidal, and antinociceptive properties akin to weak opioids, *C.striata* extract serves as an unparalleled biological agent for the complete structural regeneration of purulent ulcerations.[22,27]

Snakehead fish albumin offers a comprehensive range of therapeutic benefits, most notably in wound healing and tissue repair, where it accelerates post-surgical recovery by promoting fibroblast proliferation and enhancing collagen synthesis.[28] Beyond physical recovery, it provides vital nutritional and clinical support by treating hypoalbuminemia, combating severe malnutrition, and maintaining the blood oncotic pressure.[6] The albumin also exhibits strong anti-inflam-flammatory properties that reduce edema and swelling while modulating pro-inflammatory cytokines.[29] This is complemented by its antioxidant activity, albumin has antioxidant properties due to its ability to scavenge the free radicals and protects tissues from oxidative stress.[29,30] Furthermore, it serves as an immunomodulator by boosting the overall immune system response and enhancing white blood cell function.[31]

Based on mitogenic cytokine profile parameters, administration of snakehead fish extract was shown to significantly stimulate cells at the injury site to secrete TGF-β1 at a much higher intensity.[28] This increase in cytokine expression is essential because TGF-β1 acts as an inducer that compels keratinocytes at the wound margins and fibroblasts to enter a proliferative division cycle that stimulates massive cellular migration.[6]

In terms of immunology and vascular architecture, *C.striata* albumin facilitates a smooth regenerative transition to prevent wounds from becoming stuck in a prolonged state of exudative inflammation.[29,32] This extract promotes the repolarization of immune cells by accelerating the reduction of pro-inflammatory macrophages in the

advanced phase of inflammation to ensure the achievement of final healing resolution.[29,32] Concurrently, vascular modification occurs, wherein pro-angiogenic stimulating activity drives the growth of new capillaries in the early granulation phase. This process is then naturally followed by the elimination of excess capillaries upon entering the maturation or remodeling phase.[6]

The combined regenerative, anti-inflammatory, antioxidant, and angiogenic actions of *S.hermanii* and *C.striata* in oral wound healing are summarized in Fig.1.

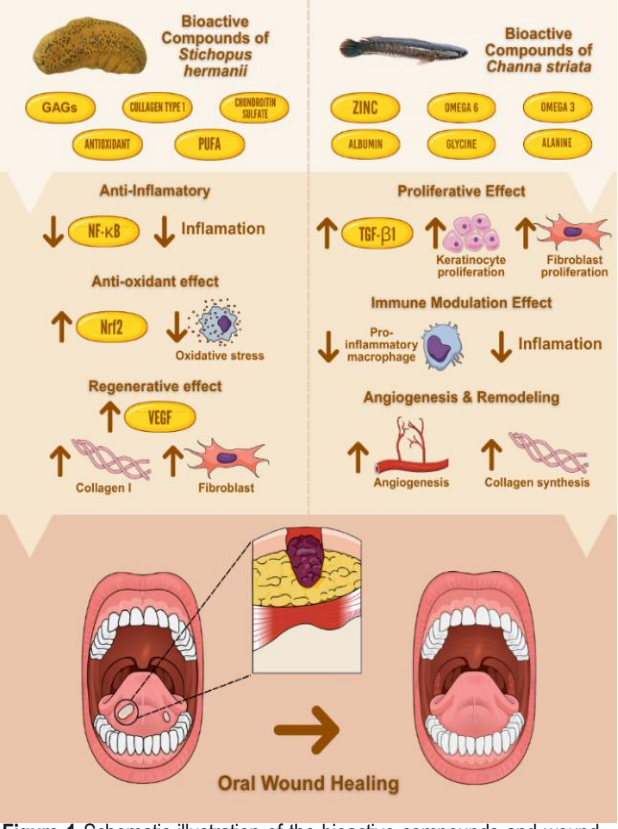

Figure 1 Schematic illustration of the bioactive compounds and wound-healing mechanisms of *S.hermanii* and *C.striata* in oral mucosal repair.

Microneedle technology for drug delivery

Pharmacological delivery systems and biotechnology for macromolecule release have undergone a structural revolution over the past two decades with the introduction of microneedle architecture. This technological concept, which combines the user-friendly, non-invasive profile of conventional transdermal *patches* with the absolute instantaneous systemic bioavailability of hypodermic needles, represents the most vital paradigm shift in the field of precision drug delivery engineering.[33,34] Morphologically, the microneedle matrix is designed as a polymer *backing layer* adorned with thousands of microscopic needles or spikes, each of which is engineered to have a height within ultra-fine parameters, typically ranging precisely between 100 and 1,000 µm.[35] This micro-scale architectural design targets the primary functions of skin and epithelial penetration: these spikes are physically designed to tear through the barrier of the epithelial membrane or the lipophilic barrier of the skin's stratum corneum; however, their penetration stops precisely just before reaching the nerve endings (nociceptors) and the dense vascular plexus in the dermis or lower stroma.[36] The result of this geometric engineering is the formation of a temporary micro-mechanical pathway to the capillary region of the interstitial circulatory network, achieved without any sensation of pain (painless injection).[34,37]

Classification and polymer matrix formulations

Microneedle technology has evolved into five technical variants: solid, hollow, coated, hydrogel-forming, and dissolving microneedles.[38] For oral mucosal therapy, the medical industry focuses exclusively on dissolving and hydrogel-forming microneedles because their hydrophilic carbohydrate or amino acid bases ensure a 100% biocompatibility profile.[34] These non-toxic, biodegradable, and biocompatible materials possess a structural design that guarantees high clinical safety.[39] They eliminate hazardous factors such as the risk of needle fracture during insertion, local irritation, foreign body response, and long-term tissue accumulation, which are commonly associated with solid microneedles made from metal or silicon.[40]

During manufacturing, these dissolving microneedles are formulated using medically certified, highly tolerable biopolymers such as polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), carboxymethyl cellulose (CMC), chitosan, gelatin peptides, and pure hyaluronic acid (HA).[34,40] These polymer matrix is combined with active substances. Several proteins and peptides, such as ovalbumin, insulin, viral vaccine agents, interferon-α-2b, and polymyxin B, have been successfully formulated into dissolving microneedle systems through a fabrication process carried out at room temperature, thereby preserving the activity of proteins and peptides that are sensitive to temperature changes.[41]

When injected under constant pressure into the moist oral mucosa, the polymer matrix rapidly absorbs the available exudate water, triggering an immediate, exponential swelling mechanism that gradually breaks down the matrix bonds until it completely dissolves.[42] This pharmacokinetically programmed physical lysis allows the pure therapeutic macromolecules to diffuse immediately into the tissue stroma without encountering epithelial resistance. Ultimately, this mechanism creates direct intratissue drug flow kinetics that completely bypass aggressive salivary enzymatic degradation and eliminate the liver's first-pass metabolic effect, ensuring maximum therapeutic efficacy.[33,35]

Table 1 shows outlines of the classification and formulation of polymer matrices in microneedle technology, along with their applications for oral mucosal therapy. Technologically, these microneedle devices have evolved into five distinct technical variants. However, the medical industry currently focuses exclusively on the use of dissolving microneedles and hydrogel-forming microneedles specifically for the oral cavity. This choice is well-founded because both types are made from 100 percent biocompatible biological polymers, leaving no hazardous factors.

Clinical significance of transmucosal administation in tissue regeneration

Beyond acting as a passive delivery route, the physical insertion of microneedles creates highly precise mechanical microtrauma at the basal lamina. This controlled stimulation, widely known as *percutaneous collagen induction therapy* (PCIT), acts as an intelligent biological that triggers a local inflammatory cascade to reactivate the stalled wound repair phase.[36,42] In response to these microlesions, the tissue releases chemotactic factors that force dormant fibroblasts to rebuild type III collagen and stimulate endothelial growth factors for new capillary expansion, ultimately restoring vital oxygen and nutrient perfusion.[42]

Table 1 Classification and polymer matrix of formulations

Parameter/Aspect	Description and Characteristics	Source
Microneedle Classification	solid, hollow, coated, hydrogel-forming, and dissolving microneedles	38
Main Focus of Oral Mucosal Therapy	Use is strictly limited to dissolving microneedle and Hydrogel-forming microneedle	34
Safety Profile of the Matrix	Constructed from biological carbohydrate or amino acid polymers with 100% biocompatibility.	34
Polymer Constituents (Dissolving)	Uses hydrophilic biopolymers such as PVA, PVP, CMC, chitosan, peptide gelatin, and HA	43
Active Ingredients (Molecular Cargo)	Active substances, including proteins and peptides such as ovalbumin, insulin, viral vaccine agents, interferon-α-2b, and polymyxin B, have been successfully formulated into dissolving microneedle systems.	41
Mechanism of Lysis and Drug Release	When the needle is injected into the moist mucosal interstitium, the matrix undergoes swelling (expansion due to water hydration), which disrupts the stability of the supporting matrix bonds	42
Pharmacokinetic Advantages	Stimulates the immediate diffusion of pure molecules without barrier obstruction, creating drug flow kinetics free from salivary enzymatic inhibition and completely eliminating the effects of first-pass hepatic metabolism	35

Table 2 Comparison of the dissolving microneedle patch method versus traditional mucosal topical therapy for macromolecule delivery parameters.

Pharmacokinetic Assessment Parameters	Conventional Oral Mucosal Topical Gel/Ointment	Dissolving Microneedle Patch System	Source
Tissue Penetration Depth	Very superficial. The epithelium acts as the primary barrier to drug permeation, heavily influenced by the degree of keratinization and lipid content	Targeted penetration through the epithelium to the capillary depth of the lamina propria	44,45
Macromolecule Transport Capacity	Exhibit limited transport capacity for macromolecules	Capable of delivering genetic peptides, high-molecular-weight collagen proteins, and antibodies (millions of Daltons)	34,46
Drug Dosage Loss (Efficiency)	Loss of up to >90% due to saliva secretion and chewing motion	capable of penetrating the pseudomembranous barrier, allowing direct delivery of the drug to the affected site, which minimizes drug loss and significantly improves therapeutic efficacy.	34,47
Additional Regenerative Bioactivation Mechanism	None (solely dependent on diffusion absorption of the active ingredient)	Mechanical stimulation (collagen induction therapy) from microneedle punctures	48

Through a single clinical intervention, this micro-injection system delivers a highly potent dual-synergistic healing effect. On one side, the structural microtrauma mechanically regenerates the dormant healing cascade that typically prevents oral wounds from closing. Simultaneously, the infused cargo of marine collagen and albumin supplies the dense metabolic nutrients and genetic signals required to completely transform the pathological inflammatory environment into the biological architecture of absolute wound closure.[33,42]

Oral microneedle patch for mucosal applications

Translating microneedle technology to the oral cavity requires meticulous bioengineering to overcome a highly dynamic and wet mucosal environment.[42,45] The oral mucosa faces extreme fluid dynamics from constant saliva circulation, which transports aggressive degrading enzymes and is exacerbated by continuous mechanical shear stress from chewing, tongue movement, and speaking.[34] Because of these harsh physiological conditions, conventional topical therapies such as mucosal compresses, lozenges, and gels consistently fail, they are prematurely washed away and swallowed before achieving localized intralesional retention. This fundamental lack of targeted drug retention directly causes extraordinarily high rates of therapeutic failure and drastically lowers patient compliance.[34,49]

DISCUSSION

Synergistic integration of collagen and albumin in microneedle-based delivery systems for wound healing

Conventional treatments often fail to resolve the persistent inflammatory microenvironment of oral ulcers. To overcome this, an advanced hybrid bio-matrix proposes fusing hydrolyzed type I marine collagen (*S.hermanni*) with albumin and zinc extracts (*C.striata*) to create a complementary "multi-layered synergy".[35] In this system, marine collagen acts as a structural scaffold that triggers cell migration and angiogenesis, while snakehead fish albumin maintains osmotic stability, prevents tissue edema, and supplies essential nutrients to accelerate the epithelial division cycle.[36]

At the genetic level, this combination delivers a powerful two-way modulation, golden sea cucumber compounds suppress inflammation by blocking NF-κB, while albumin simultaneously stimulates TGF-β1 to trigger massive fibroblast proliferation and suppress destructive MMP enzymes.[35,36] By utilizing dissolving microneedles to create "microtunnels" through the mucosal barrier, this macromolecular cargo is delivered directly into the stroma without salivary degradation. This precise delivery transforms a stagnant wound environment into a regenerative incubator for rapid, accurate tissue closure.[43,47]

Current gaps in biomedical research

A pressing issue in primary biotechnology that has yet to be fully addressed is the gap in control over homogenization, standardization, and quality of extraction, matrix purification, and constituent isolation from bio-animal species.[50] Reports on the chemical fractionation of extracts isolated from marine animals highlight the instability of highly fragile macromolecules, which are susceptible to heat and proteolysis.[51] The abundance and efficacy of the weight fraction of pure albumin components in extracts from fresh snakehead fish and the percentage of intact helical collagen peptide molecules in the golden sea cucumber species are critically variable.[52,53] These content margins influenced by non-static determinants such as specimen location, water temperature during capture, marine ecological conditions, post-harvest metabolic stress on marine fauna, as well as the variability in the concentration of the enzymatic isolation system used in commercial wet extraction processes conducted by the researchers.[20,54] The amplitude of inconsistencies in the protein fractionation profile of this aquatic biomass is prone to compromising and diminishing the precision standards required for active pharmaceutical ingredients in clinical pharmaceuticals, which are strictly mandated by patents for synthetic tissue engineering that are molecularly harmonized in dosage.[50,54]

Critical methodological gaps also lead to conflicting issues regarding the selection of thermal heating parameters in the sterilization installation procedures for the mass production of commercial poly-

biological microneedle matrices.[55] Conventional sterilization methods, such as gamma irradiation and ozone gas fumigation, may compromise the integrity of marine albumin- and collagen-based protein matrices, potentially reducing their biological activity and therapeutic efficacy.[37] From the perspective of structural material engineering and static shear mechanics, the fabrication of wet-adhesive mucosal microneedle composite polymers from animal-derived biological extracts lacks extensive reference data regarding needle tip fracture geometry and swelling behavior in human saliva under high-tempeperature conditions.[33,34] As highlighted in the existing literature, double-blind randomized studies evaluating the safety and systemic toxicity of this topical intervention in patients with severe inflammatory conditions, immunocompromised cancer, and oral mucositis remain limited.[56] This gap compels researchers to conduct rigorous clinical monitoring of volunteers, supported by substantial funding, in order to regulate and evaluate its potential long-term immunological and anaphylactic effects.[36,56]

Vision for transformation: perspectives and directions for future evolution

The future of mucosal wound healing points toward highly advanced, personalized regenerative technologies, primarily utilizing 3D bioprinting to create adaptive, biomorphic microneedle arrays that are specifically customized to a patient's ulcer topography to ensure perfect, airtight adhesion.[42,45] Furthermore, this trajectory envisions the development of *smart stimulus-responsive bioelectronic microneedles*, which encapsulate sea cucumber and albumin biomolecules within a hydrogel nano-matrix designed to automatically detect toxic microenvironmental cues-such as acidic pH, bacterial excretions, or reactive oxygen species (ROS)-and proportionally release therapeutic agents in real-time.[36] Ultimately, if successfully developed, oral microneedle patches loaded with golden sea cucumber collagen and snakehead fish albumin may represent a paradigm shift in oral wound care, offering a precise, patient-friendly, and biologically active platform for accelerating oral mucosal regeneration. The growing number of clinical trials and commercially available microneedle-based products further highlights the significant translational potential of microneedle technology to transform future therapeutic delivery systems and clinical medicine.[57]

It is concludes that conventional topical therapies for oral mucosal wound healing are often limited by saliva-induced washout and epithelial barrier resistance. Oral microneedle patch technology offers a promising alternative by enabling precise transmucosal delivery of therapeutic agents directly into target tissues without stimulating pain receptors. This approach combines marine collagen from the golden sea cucumber (*S.hermanni*), which serves as a structural scaffold and suppresses NF-κB-mediated inflammation, with albumin from the snakehead fish (*C.striata*), which maintains osmotic balance, supplies essential nutrients, and enhances TGF-β1 release to promote cell proliferation and tissue repair. Despite its significant therapeutic potential, clinical translation remains challenged by the need for standardized biomaterial extraction and sterilization methods that preserve protein integrity. Future oral microneedles are expected to evolve into personalized 3D-bioprinted patches with smart bioelectronic capabilities that autonomously respond to inflammation and wound pH changes.

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