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# Investigation of the molecular alterations associated with the efficacy of microneedling therapy and its potential applications in medical and dental practices

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**ABSTRACT**
Microneedling is an emerging minimally invasive technique that induces microscopic wounds in the skin or oral mucosa, stimulating healing and rejuvenation through complex biological processes. This review examines the impact of microneedling on inflammation, highlighting its role in fibroblast activation, modulation of cytokine release, neovascularization, and regulation of matrix metalloproteinase activity. By engaging these pathways, microneedling facilitates tissue remodeling and enhances the skin's regenerative capacity, making it beneficial for various conditions such as wound healing, skin rejuvenation, and periodontal therapy. Recent technological advancements in microneedling, including its application for targeted drug delivery and incorporation of biologically active compounds, hold promise for future clinical use. Understanding the mechanisms underlying the therapeutic effects of microneedling can help optimize treatment strategies, maximize clinical outcomes, and minimize side effects.
**Keywords**: microneedling; inflammation; tissue regeneration.

## INTRODUCTION

### Microneedling

Microneedling (MN), also known as percutaneous collagen induction therapy, involves creating small channels in the skin with tiny needles and is primarily used for aesthetic and therapeutic purposes. Since the procedure is minimally invasive, only a few contraindications, such as ongoing treatment for malignancies, active viral infections of the skin or mucous membranes, and active inflammation at the puncture site, disqualify a patient from the procedure. Patients are qualified for MN based on a combination of subjective assessment and physical examination, guided by international standards for dermatosurgical procedures. This process typically involves taking a patient's medical history, thoroughly examining the treatment area, and assessing the need for anesthesia [1].

Microneedling therapy is generally safe; however, it carries potential risks and complications that depend on factors such as the patient's skin type, the technique used, and adherence to aftercare instructions. Common temporary side effects include redness, swelling, mild pain, and skin irritation [2, 3]. Rare but more persistent adverse effects include post-inflammatory hyperpigmentation, tram-track scarring, and granulomatous reactions. Factors that may increase the risk of complications include active skin infections, darker skin types, and metal allergies [2]. The safety of home MN rollers remains a significant concern, as home devices, unlike professional ones, are retracted from the skin at a different angle than the entry angle, causing microtears. These microtears can contribute to the spread of skin infections and the formation of undesired scar tissue.

Given these risks and evolving regulatory guidelines, dermatologists and aesthetic medicine doctors play a key role in educating patients on the risks associated with MN devices and encouraging professional consultation when needed [4]. Because of its potential to upregulate genes associated with tissue remodeling, epithelial proliferation, reduction of pro-inflammatory cytokines, and promotion of the skin's natural repair processes [5], MN has drawn significant attention in dermatology and plastic surgery for its ability to: heal wounds [6], rejuvenate skin [7], treat androgenetic alopecia [8], and reduce inflammation in long-term skin damage by administering pharmaceutical compounds directly to affected regions [9].

In addition to drug delivery, microneedles have been explored for biosensing, body fluid extraction, and nerve stimulation applications [10]. Hydrogel-forming microneedles have shown potential in various dental applications, including local anesthesia, oral ulcer management, and periodontal treatment [11]. In dentistry, MN can help treat conditions such as gingival recession, periodontal defects, and soft tissue healing after surgery or trauma [12, 13].

Several MN techniques exist, with the choice depending on the treatment area and the intended therapeutic outcome. The MN device is gently rolled, stamped, or placed across the treatment area, creating a series of microscopic punctures. The depth of MN-induced damage can be classified as mild, moderate, or deep, depending on the needle length [14]. Commonly utilized microneedle lengths range 1.0–2.5 mm, with a depth of 2.5 mm often yielding the most

favorable therapeutic outcomes for acne scar treatment [15]. However, 1.5 mm is the predominant depth reported in the literature for gingival depigmentation and inflammation treatment [16, 17]. Microneedles can be fabricated from diverse materials such as metal, silicon, ceramic, and polymer, each offering distinct properties and advantages [18]. A wide range of mechanical MN devices, including rollers, pens, pins, and nanopatches, are approved for use by the United States Food and Drug Administration [19, 20].

Microneedling can be traced back to 1905, when German dermatologist Ernst Kromayer first recorded the use of this procedure. Since then, the method has been improved and applied in many areas of biomedicine. Nonetheless, the precise mechanisms underlying the modulation of inflammatory processes by MN are not fully understood, particularly those associated with the health of the oral cavity [21].

### Inflammation

Inflammation is a common physiological defense mechanism employed by the organism in response to potentially harmful stimuli. Activated macrophages, dendritic cells, and mast cells, through the engagement of intracellular signaling cascades, synthesize eicosanoids and cytokines, which act as pivotal mediators of the inflammatory process [22]. The inflammatory response typically involves a series of overlapping stages, including the recognition of harmful stimuli, vasodilation and increased vascular permeability, recruitment of immune cells, elimination of the stimuli and inflammatory mediators, and repair and restoration of tissue function [23]. The duration and intensity of each stage can vary depending on the nature and severity of the initial insult, as well as individual factors. Acute inflammation is usually self-limiting and resolves within a few days to weeks [24].

Intracellular signaling pathways mediated by nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription (STAT), and Janus kinase (JAK) are activated when inflammatory mediators interact with their receptors, such as: the interleukin-1 receptor (IL-1R), interleukin-6 receptor (IL-6R), and tumor necrosis factor receptor (TNFR). These pathways control the inflammatory response by recruiting inflammatory cells, synthesizing cytokines, and regulating cell proliferation, differentiation, regeneration, and apoptosis [25].

The resolution phase involves the removal of the initial trigger, neutrophil apoptosis, efferocytosis, and the production of pro-resolving mediators such as annexins, lipoxins, and resolvins [26]. Following this, tissue repair processes, including angiogenesis, fibroblast proliferation, and collagen deposition, are initiated. Successful resolution and repair lead to the restoration of normal tissue structure and function [27].

## MATERIALS AND METHODS

This review, conducted in accordance with the PRISMA guidelines [28], aims to provide a thorough and comprehensive synthesis of the current evidence on the molecular alterations associated with the efficacy of MN therapy and its potential applications in medical and dental practices. The search was performed in the PubMed database using the keywords: "microneedling inflammation", "microneedling molecular alterations", "microneedling therapy", and "microneedling dentistry". The literature search covered the period from 1996 to November 2, 2024.

The following inclusion criteria were applied: (1) prospective clinical trials; (2) retrospective clinical trials; (3) *in vivo* studies; (4) *in vitro* studies; (5) studies published in English; (6) case reports; and (7) meta-analyses. Articles were included if they investigated MN therapy and its potential applications based on molecular alterations and evaluated the accuracy and reliability of existing reports.

The exclusion criteria were as follows: (1) papers related to MN but not molecular alterations after MN therapy; (2) observational studies; (3) research on aspects of MN treatment for chronic inflammatory skin disorders; and (4) unreviewed literature (Fig. 1). Duplicate articles were removed by exporting the retrieved references to Zotero software version 6.0.36.

Two independent reviewers (E.P. and M.K.) screened the remaining articles by evaluating their titles and abstracts. The full-text versions of the selected articles were then assessed to confirm the inclusion of relevant studies. Any discrepancies were resolved through consensus or discussion with an additional investigator (P.K.).

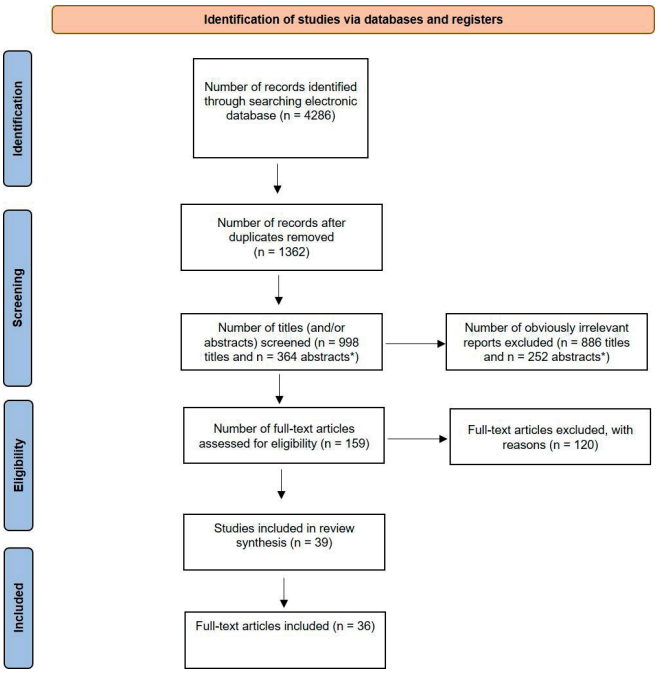



**FIGURE 1.** Summary of the search and selection of studies related to microneedling

## RESULTS

The main inflammatory processes modulated by MN include cytokine synthesis, fibroblast activation, neovascularization, matrix metalloproteinases (MMPs) activity, and tissue remodeling (Fig. 2). Stimulation of these processes and pathways is essential for both short-term healing and long-term improvement in tissue quality.

## Microneedling-modulated cytokine synthesis

Disruption of the epidermis and dermis has been shown to stimulate cellular proliferation and migration through the activation of growth factors and cytokines, including platelet-derived growth factor, transforming growth factor (TGF) β and α, connective tissue activating protein, connective tissue growth factor, and fibroblast growth factor [29]. These substances play a crucial role in the skin's regenerative response, promoting the repair and rejuvenation of the treated area. In general, skin disruption contributes to inflammation development, including cytokine production and attraction.

However, MN treatment in a 3D skin model (Matriderm-bovine collagen–elastin matrix) decreased the messenger ribonucleic acid (mRNA) expression of proinflammatory cytokines such as: IL1α, IL1β, IL24, IL36γ, and IL36 receptor antagonist. It also caused upregulation of C-C motif chemokine 11, a cytokine involved in immune cell recruitment [5]. Furthermore, MN likely plays an important role in upregulating TGF-β3, an anti-fibrogenic isoform associated with scarless wound healing [25, 26]. In models using silk fibroin microneedle patches, the treatment downregulated the expression of TGF-β1 [27].

Recent studies have demonstrated that a new treatment strategy based on microneedles loaded with matrine, a natural Chinese medicine product with proven anticancer, anti-inflammatory, and antiviral effects, decreased the levels of cytokines such as: IL-6, IL-1β, IL-17, and TNF-α in eczema cells and animal models [30].

## Microneedling-modulated neovascularization

Cytokines released by disrupted tissue attract monocytes and neutrophils, which release mediators such as vascular endothelial growth factor A, fibroblast growth factors, and angiopoietins to stimulate microvascular endothelial cells [31]. Newly formed blood vessels supply oxygen and nutrients to the inflamed tissue, promoting regeneration.

Microneedling has been shown to enhance the viability of skin flaps by promoting neovascularization and expanding vascular structures in the papillary dermal layer [32]. A study by Cao et al. demonstrated that their dissolvable microneedle-based wound dressing for transdermal delivery of platelet-derived exosomes, tested in a rat model of diabetic wounds, increased the number and diameter of blood vessels in the treated area. This effect may have been a result of the observed differentiation of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype [33]. M2-like macrophages produce anti-inflammatory cytokines and contribute to tissue remodeling, neovascularization, and resolution of inflammation [34].

## Microneedling-modulated matrix metalloproteinase expression

Matrix metalloproteinases are a large family of enzymes that break down proteins. In addition to their role in extracellular matrix degradation, they play crucial roles in cellular communication, immune system modulation, and gene expression. Matrix metalloproteinases influence tissue remodeling, including abnormal scar formation, and are integral to wound healing [35]. Dysregulation of MMPs can contribute to various diseases [36].

Research using a novel skin tissue model has shown that the level of matrix metalloproteinase 1 (MMP-1) gradually increases over 6 days following MN treatment [37]. Matrix metalloproteinase 1 serves as an anti-fibrogenic agent by reducing scar formation, and its elevated levels enhance tissue regeneration in skin with higher epithelial hyperplasia [38]. In the 3D skin model, Schmitt et al. observed the upregulation of tissue inhibitor of matrix metalloproteinases 3 (TIMP3), which may be beneficial for treating or preventing hypertrophic scar formation. Additionally, Schmitt et al. reported that MN activated genes associated with collagen synthesis, including *TIMP3*, *COL3A1*, and *COL8A1* [5]. These genes are responsible for the synthesis of collagen type 3, which increases during the early stages of wound healing [39], and collagen type 8, an extracellular protein expressed in tissues undergoing active remodeling [40]. Tissue inhibitor of matrix metalloproteinases 3 also contributes to the stabilization of basement membranes, tissue remodeling, and angiogenesis during wound healing [41].

Moreover, MN creates microchannels in the skin, facilitating the delivery of therapeutic agents such as doxycycline, which can further modulate MMP activity [42] and activate MMP-responsive properties, enabling faster drug delivery [5].

## Microneedling-modulated fibroblast activation and tissue remodeling

The mechanism by which MN induces fibroblast activation has been extensively studied. It is postulated that the microlesions created by the needles deceive the organism into perceiving a genuine tissue injury, thereby triggering the classic wound-healing cascade [43]. Upon tissue injury, fibroblasts differentiate into myofibroblasts, which mediate large contractions and actively synthesize extracellular matrix proteins. This leads to the induction of collagen production and contributes to the wound-healing process [44].

Studies have demonstrated that MN activates genes associated with tissue remodeling (*TIMP3*, *COL3A1*, *COL8A1*), cellular

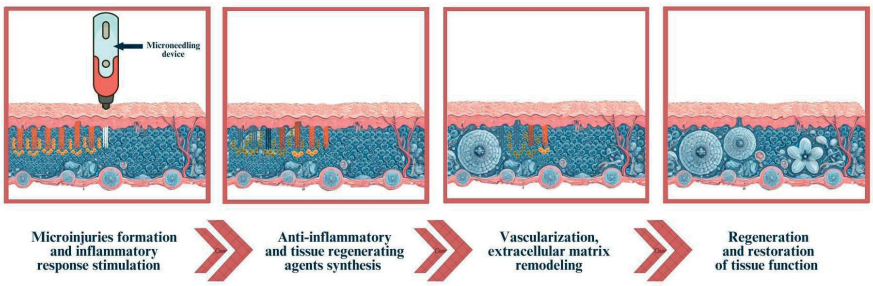
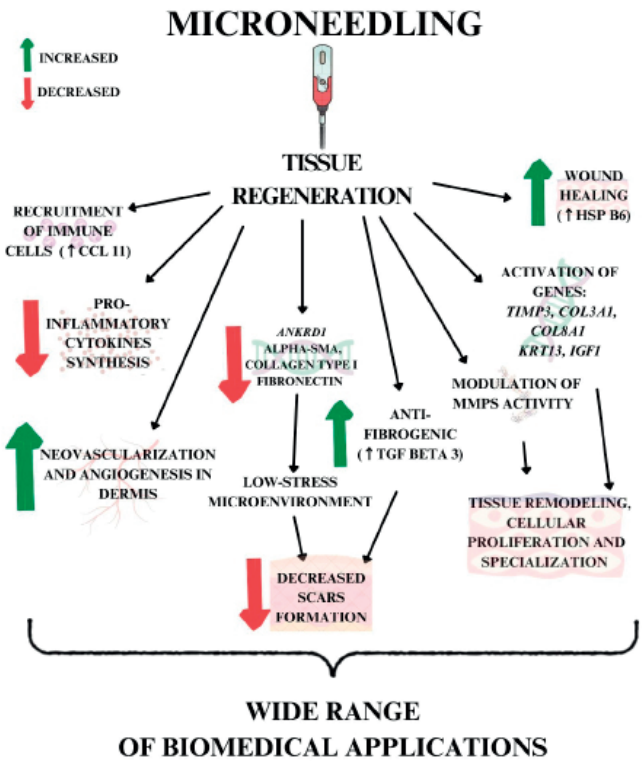



**FIGURE 2.** Tissue regeneration and healing triggered by microneedling (while entering the skin, the device forms micro-injuries that initiate an inflammatory response; in microneedling treatment, this response contributes to regeneration and the restoration of physiological tissue function)

proliferation, and specialization, such as *KRT13* and *IGF1*. It also increases the expression of heat shock protein B6, which plays a role in wound healing [5]. Research using a silk fibroin microneedle patch in a rabbit ear hypertrophic scar model showed enhanced ultimate tensile strength toward skin normalization and a significant reduction in the scar elevation index. Microneedling reduced fibroblast-generated contraction and mechanical stress by decreasing the expression of *ANKRD1*, a mechanically sensitive gene. The treatment also lowered the production of alpha-smooth muscle actin (α-SMA), collagen type I, and fibronectin, which are upregulated in response to mechanical stress characteristic of hypertrophic scar formation [45] (Fig. 3). This resulted in a low-stress microenvironment that significantly reduced scar production [46].

In studies using 3D skin models, complete tissue regeneration following MN was achieved within 5 days [5]. Furthermore, the combination of MN and probiotic extracellular vesicle therapy has shown beneficial effects on wound healing when applied to infected sites. These effects are attributed to enhanced keratinocyte and fibroblast activities, improved vascularization, and modulation of collagen deposition [47].




CCL 11 – C-C motif chemokine 11; alpha-SMA – alpha-smooth muscle actin; TGF beta 3 – transforming growth factor beta-3; HSP B6 – heat shock protein family B (small) member 6; *IGF1* – insulin-like growth factor 1 gene; *TIMP3* – tissue inhibitor of metalloproteinases 3 gene; *COL3A1* – collagen type III alpha 1 chain gene; *COL8A1* – collagen type VIII alpha 1 chain gene; *KRT13* – keratin 13 gene; *ANKRD1* – ankyrin repeat domain 1 gene

**FIGURE 3.** The wide range of biochemical processes modulated by microneedling underlying its multidisciplinary use in biomedicine (microneedling introduces controlled and targeted inflammation by recruiting immune cells, decreasing proinflammatory cytokine levels, and regulating collagen synthesis and degradation; these processes promote neovascularization and angiogenesis and exhibit an anti-fibrogenic effect, contributing to tissue remodeling, improved wound healing, and decreased scar formation)

## DISCUSSION

Microneedling elicits an inflammatory response, initiating the normal post-inflammatory chemical cascade. Its regulated and minimally invasive nature makes it a flexible and promising modality for administering anti-inflammatory agents to the skin and oral mucosa. These findings suggest that MN is a versatile technology with a wide range of biomedical applications, from wound healing to drug administration (Fig. 3). Periodontologists might use this technique, in combination with a coronally advanced flap, as a treatment for type 1 recession defects in patients with a thin gingival phenotype [48]. Additionally, MN reduces gingival inflammation in patients with gingivitis [16]. This effect may be related to the modulation of MMP expression observed after MN. Dysregulated MMP activity is associated with numerous oral diseases, including the tissue destruction characteristic of periodontal diseases [49]. Therefore, the downregulation of MMPs may represent a promising approach to preventing periodontal disease or could play a crucial role in its treatment. Furthermore, MN has proven effective as a safe method for administering local anesthetics in dental procedures [50].

By forming microchannels and modulating the extracellular matrix, MN facilitates the delivery of drugs such as antibacterial agents (e.g., peptide FK13-a1, doxycycline), salicylic acid [42, 51], and anti-inflammatory agents, which may be beneficial in the treatment of rheumatoid arthritis [52]. The polarization of macrophages into the anti-inflammatory M2 phenotype following MN treatment promotes angiogenesis, extracellular matrix remodeling, and tissue regeneration [52]. Current research has also demonstrated that MN patches can be employed to deliver exosomes containing microRNA-29b (miR-29b) mimics. MicroRNA-29b exhibits antifibrotic activity, which, when introduced into cardiac tissue following myocardial infarction, reduces inflammation, decreases infarct size, inhibits fibrosis, and improves organ function [53]. Additionally, MN can serve as a delivery system for bevacizumab, a monoclonal antibody that functions as an angiogenesis inhibitor [54], offering a more efficient treatment compared to conventional methods [55].

## CONCLUSIONS

As the field continues to advance, further developments in microneedle design, fabrication, and clinical applications are anticipated [56]. This ongoing innovation holds immense potential for enabling breakthroughs and addressing unmet needs within biomedical technology. Microneedle-based devices could revolutionize drug delivery, diagnostics, and treatments, including for oral cancers, and the administration of painless local anesthesia [57]. To fully elucidate the mechanisms underlying MN's therapeutic properties and expand its use into new areas of medicine, further research is warranted.

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