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The therapeutic potential of herbal-infused microneedle formulations and their pivotal role in disease treatment

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Abstract

Microneedle (MN) technology has revolutionized healthcare by seamlessly integrating with the natural healing properties of herbs, presenting a ground-breaking approach. The incorporation of herbal ingredients into microneedle formulations offers a plethora of benefits, capitalizing on the power of nature for enhanced skin penetration and heightened therapeutic efficacy. Multilayer fibroparticle MNs induce superficial bleeding at low levels, causing controlled micro-injuries in the skin without damaging the epidermis. The aforementioned process initiates a cascade of events that ultimately results in the secretion of growth factors, such as platelet-derived growth factor (PGF), transforming growth factor alpha and beta (TGF- α and TGF- β), connective tissue activating protein, connective tissue growth factor, and fibroblast growth factor (FGF). The anti-inflammatory and soothing attributes of herbal constituents make MN formulations, a gentler alternative to synthetic counterparts addressing medical concerns such as acne, hyperpigmentation, and ageing while promoting overall skin health. The herbal-infused MN exhibits significant promise aligning with the increased demand for sustainable and eco-friendly options. Beyond skincare, the herbal MN has therapeutic potential in treating various diseases. Various herbal compounds available in MN include Neem, Lavender oil, Ginseng, *Aloe vera*, Green tea, Curcumin, *Centella asiatica*, *Premna serratifolia*. Integrating herbal products into microneedles adds a unique dimension, merging modern science with traditional wisdom. Herbal extracts enhance drug delivery efficacy, reduce side effects, and tap into the benefits of natural remedies. The synergy between diverse microneedle and herbal products opens new frontiers in drug delivery, improved treatment outcomes, and enhanced patient well-being. The present paper provides an in-depth analysis of the multifarious aspects of microneedle technology, highlighting its crucial role in shaping the future of the pharmaceutical industry.

1. Introduction

The skin our body's largest sensory organ serves as a protective barrier against various harmful micro-organisms which is essential for the management of overall health (He *et al.*, 2021). Skin damage resulting from trauma, burns, hazardous chemicals, genetic conditions, or systemic illnesses poses severe risks to people's well-being. Hemostasis, inflammation, granulation, and tissue remodeling are all important steps in the complicated process of wound healing; any interruption in this order might impede the healing process. Biomaterials are engineered to function in harmony with biological processes, utilizing the body's innate capacity for healing to promote the regeneration of tissues or organs (Othman *et al.*, 2018).

The two most commonly used techniques for administering drugs through the skin are topical lotions and hypodermic needles. Nevertheless, patients may experience pain from needles, and creams sometimes have a low bioavailability. The stratum corneum, middle epidermis, and deepest layer of dermis make up the skin, which acts as the first barrier for topical drug administration. A substantial

barrier, the stratum corneum only permits certain compounds with low molecular weight and lipophilic characteristics to pass through (Singh *et al.*, 2023). This limited permeability poses challenges in formulating effective topical medications. To enhance medication permeation, various techniques for topical or transdermal administration were explored including topical gels, transdermal patches, and microneedles (Prausnitz *et al.*, 2008; Gupta *et al.*, 2012; Singh *et al.*, 2020).

Microneedles is an innovative and evolving technology in the branch of medical and pharmaceutical science that has gained considerable attention in recent years. These microscopic devices are designed to painlessly and minimally invasively puncture the skin, creating controlled micro-channels that do not damage the outermost layer, known as the epidermis. This introductory statement signifies the profound potential of microneedles as a versatile tool with a wide range of applications, including target drug delivery, diagnostics, and even cosmetic procedures (Kushwaha *et al.*, 2010). As we explore the intricacies of microneedles further, it becomes evident that their unique capabilities hold promise for transforming various aspects of healthcare and beyond.

2. Benefits of microneedles

Microneedles offer a host of benefits due to their unique properties and applications, and here is a detailed exploration of some of those advantages:

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- i. Minimally invasive:** Microneedles create micro-channels in the skin, which are typically painless and cause minimal discomfort. This minimally invasive approach is less intimidating to patients compared to traditional needles, making it ideal for various medical procedures.
- ii. Enhanced drug delivery:** Microneedles facilitate precise and controlled drug delivery. They can be used to administer a wide range of pharmaceuticals, from insulin to vaccines, with improved absorption and bioavailability which is beneficial for patients who frequently take injections.
- iii. Reduced side effects:** The controlled release of drugs using microneedles reduces the side effects that are related to traditional injections which significantly enhances patient compliance and comfort.
- iv. Diverse applications:** Microneedles are versatile and find applications in various fields, including dermatology, diagnostics, and cosmetic procedures. They can be used for skin treatments, transdermal drug delivery, and even as biosensors for monitoring health parameters.
- v. Elimination of needle phobia:** Fear of needles is a common issue among patients. Microneedles, due to their painless nature, help in reducing this anxiety and improve patient adherence to medical treatments.
- vi. Targeted therapy:** The ability to design microneedles with specific shapes and sizes for targeted drug delivery to particular skin layers or tissues. This is advantageous for conditions that require localized treatment.
- vii. Cost-effective:** Microneedles are often cost-effective in the long run. They reduce the need for specialized healthcare professionals to administer treatments and controlled drug release can potentially lead to lower drug doses.
- viii. Improved vaccine delivery:** Microneedles have shown promise in vaccine administration. They can enhance vaccine effectiveness, reduce the risk of contamination, and eliminate the need for refrigeration, which is particularly valuable in remote or resource-limited areas.
- ix. Patient convenience:** The self-administration potential of microneedles, such as wearable patches, can enhance patient convenience and reduce the burden on healthcare systems.
- x. Enhanced cosmetic procedures:** Microneedles are employed in cosmetic dermatology for procedures like skin rejuvenation and scar reduction. They promote collagen production and skin regeneration, providing non-surgical alternatives to traditional cosmetic treatments.
- xi. Precision medicine:** The ability to design microneedles with specific shapes and sizes allows for personalized medicine. In diseases where individualized drug delivery is essential, such as cancer treatment, microneedles offer a platform for tailoring treatments to a patient's unique needs.
- xii. Emergency medicine:** Microneedles are being explored in emergency medicine for the rapid and painless administration of medications, such as antidotes, in situations where every second counts.

xiii. Chronic disease management: For chronic disease patients like rheumatoid arthritis, where regular medication is necessary, microneedles can simplify this treatment regimens, improve adherence, and enhance the overall quality of life.

xiv. Wearable drug delivery devices: Microneedle-based wearable patches are being developed, allowing patients to self-administer medication. This innovation increases patient convenience and reduces the burden on healthcare systems.

xv. Local treatment: Microneedles can be tailored for localized treatment. In dermatology, they are used to treat skin conditions such as psoriasis and acne. The controlled release of medications directly at the site of the disease minimizes systemic side effects.

xvi. Transdermal drug-delivery: MNs allows transdermal drug delivery which can be a game-changer in situations like CVS diseases where medications are absorbed into the bloodstream steadily over time. Microneedles offer a painless and non-invasive alternative to oral medications by-passing issues related to gastrointestinal absorption and potential side effects.

Thus, we can say that microneedles have opened up new avenues in disease treatment by providing a painless, controlled, and patient-friendly approach to drug delivery. Their application is not limited to a specific medical field and they have a lot of potential to help manage a variety of diseases by increasing patient compliance, lowering side effects, and improving treatment outcomes.

3. Microneedles with herbals plants or compounds

Natural products are often preferred in medicinal applications due to their lower toxicity and reduced potential for irritation. However, a considerable number of herbal therapeutics encounter challenges such as solubility, permeability, and stability issues, impacting their oral bioavailability (BA) (VM *et al.*, 2023).

Herbal or natural excipients offer significant advantages compared to their synthetic counterparts, being non-toxic, cost-effective, and readily accessible (Singh *et al.*, 2016; Kim *et al.*, 2012). The growing awareness of these herbal excipients, primarily derived from natural polymers, is leading pharmaceutical industries to increasingly favor their utilization in formulation development (Tiwari *et al.*, 2020; Mohd, 2021).

The advancement of phytochemistry utilizing bioactive components extracted from fruits has resulted in the discovery of a novel chemical with a broad spectrum of pharmacological properties. To attain therapeutic benefits, enhance human health, and promote overall wellness, these bioactive and raw fruit components, in various forms such as formulated, juiced, or extracted, are being consumed and utilized. The research on phytochemistry and fruit bioactive components has shown immense potential for the improvement of human health. The benefits these natural compounds provide are remarkable. The development of innovative treatments and therapies utilizing these compounds is a significant step forward in the healthcare industry. It is noteworthy that the application of fruit bioactive components is still in its nascent stages, and further research is required to fully explore their potential. As such, it is interesting to see the forthcoming breakthroughs in the field of phytochemistry (Chellamal, 2022).

Table 1: Examples of microneedles containing herbals with their uses and clinical significance

S.No.	Herbal drug	Drug function	MN clinical significance containing the herbal drug
1.	Neem microneedles	Neem, a well-known medicinal plant in traditional medicine, has been explored for its anti-microbial and anti-inflammatory properties.	Microneedles containing neem extracts were developed for skin conditions such as acne and related ailments.
2.	Lavender oil microneedles	Lavender oil, recognized for its calming and stress-reducing properties.	Lavender oil was incorporated into microneedles to create a non-invasive aromatherapy delivery system. These microneedles aim to provide relaxation benefits when applied to the skin.
3.	Ginseng microneedles	Ginseng, a traditional herbal remedy known for its potential cognitive and energy-boosting effects.	Ginseng was considered for transdermal delivery through microneedles. This application has the potential for fatigue management and mental clarity.
4.	<i>Aloe vera</i> MNs	<i>Aloe vera</i> has various properties such as soothing and healing properties.	It was incorporated into microneedles for skin regeneration and wound healing applications. These microneedles were designed to enhance the delivery of beneficial compounds.
5.	Green tea extract microneedles	Microneedles containing green tea extracts, rich in polyphenols with potential health benefits such as in weight loss, liver disorders, diabetes, Alzheimer's disease.	When applied to the skin, these were explored for their antioxidant and antiageing properties.
6.	Curcumin microneedles	Curcumin, the active compound in turmeric known for its anti-inflammatory and antioxidant properties (Naikodi <i>et al.</i> , 2021).	Curcumin has been incorporated into microneedles. These microneedles aim to deliver curcumin for skin conditions or localized pain management (Sivakumar <i>et al.</i> , 2022).
7.	<i>Centella asiatica</i>	Also known as "Gotu Kola," it is recognized for its anti-inflammatory and wound healing properties, making it a popular choice for skin-care and dermatological applications.	It can potentially enhance the effectiveness of treatments for conditions such as acne scars, stretch marks, and other dermatological issues.
8.	<i>Premna serratifolia</i>	This substance has a wide range of applications, including its use as a cardiogenic, hepatoprotective, anti-biotic, anticoagulant, stomachic, and antitumor.	This substance is a commonly utilized remedy for addressing a range of health issues, including inflammation, bronchitis, dyspepsia, liver disorders, piles, constipation, and fever.

To address these issues, transdermal administration has proven successful, leading to the commercialization of several herbal transdermal products. Microneedles (MNs) are increasingly being used for cutaneous delivery of herbal therapeutics, providing an effective treatment option for various skin conditions, including cancer, acne, chronic wound healing, diabetic complications, and hypertrophic scars (Tiwari *et al.*, 2019; Bariya *et al.*, 2012). Microneedles (MNs) have emerged as a promising approach to address diverse clinical needs. One such application involves the systemic delivery of potent herbal compounds to manage various disorders, including asthma, CNS disorders, and nicotine replacement. The use of MNs enables the bypassing of first-pass metabolism, leading to a faster onset of therapeutic action. MNs composed of herbal compounds also offer potential applications in aesthetic contexts for the topical delivery of herbal therapeutics to the skin. Notably, MNs have also emerged as a minimally invasive diagnostic tool, facilitating the sampling of biomarkers from plants, skin, and ocular interstitial fluid. The potential of MNs in improving healthcare in various ways is exciting and warrants further exploration. The integration of microneedles with herbal offers several advantages

and novel possibilities in the field of healthcare which includes the following:

- i. Enhanced drug delivery:** Microneedles create microchannels in the skin, allowing for precise and controlled delivery of herbal therapeutics. Herbal extracts can be formulated into microneedles, enabling efficient absorption through the skin. This synergistic approach enhances the bioavailability and effectiveness of herbal remedies, making them an attractive option for a range of diseases.
- ii. Reduced side effects:** Herbal products are known for their natural properties that tend to have lesser side effects as compared to some pharmaceutical medications. By using microneedles to deliver herbal compounds, the risk of adverse reactions is further reduced. This is specifically beneficial for patients with chronic diseases who require long-term treatment.
- iii. Targeted herbal therapy:** Microneedles can be designed to deliver herbal compounds to specific skin layers or tissues, which is valuable for localized treatment. This precision is beneficial in conditions such as joint pain, where herbal remedies can be delivered directly to the affected area.

- iv. **Complementary medicine:** The integration of herbal products with microneedles allows for complementary treatment approaches. This can be especially useful in conditions where a combination of conventional medicine and herbal remedies may be most effective, such as in managing chronic inflammatory diseases.
- v. **Chronic disease management:** Diseases like diabetes where herbal supplements are used as complementary therapies, microneedle delivery can simplify treatment regimens. Patients can administer both conventional medication and herbal products through microneedles, improving their overall quality of life.
- vi. **Patient convenience:** The development of wearable microneedle patches containing herbal extracts can empower patients to self-administer herbal treatments. This convenience promotes patient engagement and reduces the burden on healthcare systems.
- vii. **Exploration of traditional wisdom:** Integrating herbal knowledge with modern microneedle technology provides an opportunity to explore and validate the efficacy of traditional herbal remedies in a more controlled and systematic manner.

Thus, we can say that the combination of microneedles with herbal products in disease treatment holds substantial promise in disease treatment and presents an exciting synergy between modern medical science and traditional herbal wisdom. Table 1 shows some herbal plants possessing various pharmacological activities. This innovative approach offers a novel approach to drug delivery, minimizing side effects and improving treatment outcomes. This integrative method bridges the gap and potentially opens avenues for more holistic and effective disease management.

4. Advancements in plant-based microneedles

The skin is a critical barrier for the body's defense system, making it a primary focus of current research in the field of microneedles (MNs). These innovative devices play a vital role in wound healing by preventing infections and promoting tissue remodeling after skin injuries. However, traditional patches with their simple microstructures and slow drug delivery limit their effectiveness in broader medical applications (Paleo *et al.*, 2014; Ahmad and Akhtar, 2020). In contrast, MNs possess porous microstructures that enable the use of antibacterial multifunctional polymers for encapsulating growth factors or drugs allowing for sustained or controlled release. Amid the global threat of coronaviruses, the need for a safe and rapid vaccine capable of inducing a potent and enduring virus-specific immune response is apparent. MNs have emerged as a viable option for delivering anticancer drugs, chemotherapy, photodynamic therapy, and photo-thermal therapy agents to tumor (skin) sites. This minimally invasive approach enhances therapeutic efficacy (Chi *et al.*, 2020; Zhang *et al.*, 2022; Ahmad, 2023). In experiments with subcutaneous melanoma tumors in mice, cryo-microneedles deliver ovalbumin-pulsed dendritic cells produced heightened antigen-specific immune responses which slow down tumor growth compared to i.v and s.c injections of cells. Moreover, plant-based microneedles have also been studied for their potential in treating and managing various diseases (Chi *et al.*, 2020; Zhang *et al.*, 2022).

The Chinese herb microneedle (CHMN) patch is a cutting-edge product that utilizes a unique combination of herbal extracts from *Premna microphylla* and *Centella asiatica* with microneedle

microstructures to enhance wound healing. The patch incorporates sap extracted from the herbal leaves using a traditional kneading method and is solidified with plant ash derived from the brine-induced process of tofu, in a carefully designed mold. The leaves of *Premna microphylla* are rich in pectin and various amino acids, which provide the CHMN with medicinal properties such as heat-clearing, detoxification, detumescence, and hemostasis. Furthermore, the inclusion of Asiatic acid from *Centella asiatica* contributes to the patch's ability to promote the expression of relevant growth factor genes in fibroblasts, showcasing notable antioxidant, anti-inflammatory, and antibacterial activities. The CHMN has demonstrated remarkable efficacy in activities such as antibacterial action, inhibition of inflammation, collagen deposition, angiogenesis, and tissue reconstruction during wound closure. These findings underscore the potential of integrating traditional Chinese herbs with advanced technologies to revolutionize the healthcare industry and promote the widespread acceptance and development of traditional Chinese medicine in modern society (Chi *et al.*, 2021; VM *et al.*, 2023).

Centella asiatica is a powerful herb with renowned medicinal properties for wound healing. However, its effectiveness as an ointment is limited due to the challenge of penetrating deeper skin layers. To overcome this limitation, researchers have developed two types of microneedle arrays loaded with Asiatic acid (AA), the active component of *Centella asiatica*. These microneedles are designed to penetrate the skin effectively without breaking. Both types of microneedle arrays have been optimized and characterized to ensure their strength and length are sufficient to penetrate the epidermis. Biocompatibility assessments have demonstrated over 75% viability at 100% concentration for both types of needles, and both have exhibited sustained drug release over 48 h. Importantly, the hydrogel microneedle array has demonstrated a higher release of AA than the dissolving array. In an excisional rat model, the hydrogel microneedle arrays have been shown to significantly accelerate the rate of wound closure compared to the control group. These findings highlight the potential of chitosan-PVA hydrogel microneedles as a natural treatment for wound healing. The integration of traditional Chinese herbs with advanced technologies has shown great potential to facilitate the widespread acceptance and development of traditional Chinese medicine in modern society (Ryall *et al.*, 2022).

The adoption of cosmetic raw materials for medicinal applications in a microneedle patch incorporating hyaluronic acid (HA) and *Lonicerae flos* ethanol extract (LEE) has surged, driven by their environmentally friendly characteristics. *Lonicerae flos* is renowned for containing saponins, flavonoids, iridoids, and chlorogenic acids. Clinical assessments revealed that the HA microneedle patch with LEE soluble essence effectively enhanced skin moisture content. With its historical use in oriental medicine for treating febrile diseases, *Lonicerae flos* played a crucial role in significantly improving skin moisturization, particularly in the HA microneedle patch with LEE soluble essence (EG) compared to the HA microneedle patch without LEE soluble essence (CG). These findings affirm the positive impact of *Lonicerae flos* on skin moisture content and overall skin health. Notably, ongoing studies exploring compounds beneficial for skin moisturization have resulted in the active incorporation of these compounds into skincare products (Han *et al.*, 2021).

The goal of the study was to determine how well silicon MN patches, either alone or in conjunction with lipid microparticles (LMs), might

increase quercetin's *in vitro* skin penetration, an antioxidant flavonoid. Melt emulsification and sonication were used to create LMs that contained quercetin. Pig skin was subjected to emulsions containing quercetin in either free form or microencapsulated form in Franz diffusion cells; the skin could be left untreated or treated with microneedles. Using verified tape-stripping and bead mill homogenization techniques, HPLC was used to quantify the flavonoid content of the stratum corneum and viable epidermis, respectively. Comparative investigation showed that when the skin was treated with quercetin-loaded LMs in conjunction with microneedle arrays, as opposed to intact skin, there was a significant rise in quercetin levels permeating the stratum corneum and viable epidermis. Notably, skin penetration of non-encapsulated quercetin did not significantly enhance by microneedle skin surface perforation. Given that quercetin's principal site of action is within the epidermis, the 5.5-fold improvement in the intra-epidermal distribution of the compound via the LM/microneedle method is very significant (Duong *et al.*, 2020; Tiwari *et al.*, 2021).

Microneedle (MN)-assisted transdermal DDS has remarkable potential, and there is still a huge need for active DDS to treat Parkinson's disease. *Bacopa monnieri* solid lipid nanoparticles (SLN) in dissolvent microneedle arrays measure the plant's neuroprotective properties. Microneedle arrays offer a painless and bloodless transdermal administration method that helps drugs cross the blood-brain barrier at the appropriate concentration. For microneedle arrays filled with SLNs, several experiments were carried out, such as mechanical strength analysis, *in vitro* release studies, ex-vivo permeation investigations, skin irritation testing, histopathological research, biochemical assessments, and behavioral tests. The resulting microneedle patches demonstrated enhanced motor coordination and balance as well as mechanical strength and nonirritating qualities. They also showed a decrease in bradykinesia. This microneedle approach allows for a far lower effective dose when compared to systemic delivery devices, allowing for long-term, at-home Parkinson's disease treatment (Joy *et al.*, 2022; Saloni *et al.*, 2022).

The potency/efficacy of antibacterial microneedles composed of HA (hyaluronic acid) and GT (green tea) extract for the efficient delivery of GT offers a patient-friendly alternative to traditional sustained medication release. TDDS was developed by a fabrication process to form GT/HA microneedles for incorporating antibacterial properties. FTIR spectrometry was employed to detect any potential changes in the microneedles upon the inclusion of GT. The study successfully demonstrated the regulation of GT degradation in GT/HA microneedles by adjusting the HA composition. The release characteristics were systematically measured to evaluate the impact of varying GT ratios within the HA microneedles. This approach provided an efficient and patient-friendly means of administering GT extract through antibacterial microneedles (Park *et al.*, 2014).

5. Conclusion

Microneedles (MN) is a subject of global research as a DDS for diverse conditions, encompassing both disease treatment and vaccination. The advancement of intricate delivery systems such as MNs holds the potential to enhance the effectiveness of drug administration, leading to a reduction in the overall required dose concentration. This reduction aims to minimize potential side effects associated with drug treatments.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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