Nanomedicine in Traditional Chinese Medicine: Research Progress and Therapeutic Mechanisms for Diabetic Pressure Ulcer Healing

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Abstract: Diabetes mellitus (DM) is a global health burden characterized by chronic hyperglycemia, leading to various complications including diabetic pressure ulcers (DPUs). These ulcers are notoriously difficult to heal due to factors such as impaired wound healing, oxidative stress, infection, and neuropathy. In recent years, nanotechnology has emerged as a promising tool in enhancing drug delivery and treatment efficacy for various diseases, including DPUs. This comprehensive review aims to summarize the recent advancements in nanomedicine applied to traditional Chinese medicine (TCM) and explore its therapeutic mechanisms in accelerating diabetic pressure ulcer healing.

***Keywords*:** DPUs, Nano-TCM, nanotechnology, TCM, DM

1. Introduction

Diabetes is a chronic disease characterized by hyperglycemia, which is caused by the insufficiency of absolute or relative insulin secretion and the insufficiency of its utilization[1,2]. Diabetic pressure ulcers (DPUs) is one of the most common complications of diabetes, which is an important reason for the decline of human living standard[3, 4]. Therefore, how to promote the healing of DPUs, reduce the rate of amputation and disability, protect limb function, and improve the quality of life is an international research hotspot, and also one of the important topics in the current medical field.

Traditional treatments for PU include debridement, decompression, antibiotic therapy, and wound dressings[5, 6]. However, the granulation tissue can easily grow into the dressing, which can hinder the wound healing process. Topical drugs and sprays can lead to a large amount of drug loss during use, which leads to a decrease in drug utilization and a decrease in drug efficacy[7]. Currently, Western medicine primarily focuses on the management of blood glucose levels, infection control, enhancement of peripheral blood circulation, as well as local debridement, skin grafting, external growth factor application, surgical interventions and other treatment modalities. However, the overall therapeutic efficacy remains suboptimal with high rates of amputation and disability. According to foreign reports, the average amputation rate exceeds 20%, while deep infections result in an amputation rate exceeding 52%. The integration of systemic treatment and localized external therapy in Traditional Chinese Medicine (TCM) can expedite wound healing, diminish disability rates, and enhance quality of life. However, there is an urgent need to delve deeper into the investigation of its therapeutic mechanism. In comparison to antibiotics, TCM offers the benefits of lower toxicity and a reduced likelihood of contributing to antibiotic resistance[8]. The primary active constituents of astragalus encompass astragalus polysaccharides, astragalus saponins, and trace elements of flavonoids, among others. Astragalus polysaccharide (APS) is a biologically active macromolecule that exhibits functions such as blood sugar regulation, anti-inflammatory effects, immune modulation, and antioxidant properties[9]. After extensive research, it has been demonstrated that Astragalus polysaccharide is intricately associated with numerous factors that facilitate the healing process of DPUs[10]. The nobiletin NOB, also known as satsumanthin, is a polymethyl flavonoid extracted from the peel of citrus belonging to the rutaceae family. Research has demonstrated[11] that NOB not only enhances hyperglycemia and insulin resistance but also reduces levels of inflammatory factors such as MCP-1 and IL-6 induced by high sugar intake. Additionally, it inhibits ROS levels in mesangial cells, thereby promoting anti-inflammatory effects. However, due to its poor water solubility and low utilization rate inherent in Chinese medicine, the absorption through the stratum corneum may be hindered.

Nanotechnology operates at the atomic, molecular, and supramolecular levels for material processing technology[12]. In the 1990s, nanotechnology began to be applied in traditional Chinese medicine research. For instance, by utilizing nanotechnology to study traditional Chinese medicine, it was discovered that when common Chinese medicine bezoar is prepared on a nano scale, it exhibits strong targeting capabilities[13]. Consequently, the concept of "nano Chinese medicine" was proposed. This refers to the utilization of nanotechnology to prepare active components, active parts, active drugs and their composite systems with particle sizes less than 100 nm[14]. The preparation of nano-traditional Chinese medicine is a crucial aspect in the study of this field, necessitating careful consideration of source diversity and component complexity. Consequently, diverse nanopreparation methods are employed for different drugs, including media grinding, precipitation, film hydration, and self-assembly techniques. Through various preparation methods, nano-micelles, liposomes, nano-gels, and nano-suspensions can be formulated into different types of nanomedicines[15]. Compared to non-formulated (free drug) forms, these nanomedicines exhibit enhanced solubility, improved bioavailability, precise targeting capabilities, controlled release profiles, and are better suited for conventional drug delivery pathways[16]. This paper provides a comprehensive review of the research mechanisms employed in recent years for the preparation of nano-Chinese medicines and serves as a valuable reference for further exploration of their potential in treating DPUs healing.

2. Pathophysiology of DPUs

2.1 Pathogenesis of DPUs

DPUs are characterized by infection, ulceration, or tissue damage in the foot due to neuropathy or peripheral artery disease affecting the lower extremities[17]. The occurrence of pressure ulcers can result in the rupture of the dermal barrier, subsequently leading to erosion of the underlying tissue [18]. In more severe cases, this tear may extend to involve muscle and bone. The primary etiologies for pressure ulcers include insufficient arterial blood supply, neuropathy, musculoskeletal deformities, among others[19].

2.2 The primary determinant of impaired wound healing

In patients with diabetic pressure ulcers, the presence of deactivated tissue serves as an infected lesion that impedes cell migration necessary for proper cell regeneration, thereby hindering the healing process in the affected area. Chronic non-healing diabetic pressure ulcers exhibit a prolonged inflammatory phase of healing due to a persistent inflammatory environment facilitated by heavily colonized organisms and impaired blood supply. The abundance of inflammatory cells and mediators confirms the presence of inflammation during this stage of healing. At this point, there is a rapid increase in matrix metalloproteinases and inflammatory cytokines, which promote the regulation and chemotaxis of inflammatory cells; however, it also attracts additional inflammatory cells.

3. Role of TCM in Diabetic Pressure Ulcers

Chinese medicine has a rich historical background in comprehending the therapeutic effects of pressure sore treatment. In recent years, scholars have conducted a series of studies that integrate TCM theory with extensive clinical practice to explore the healing potential of TCM for diabetic pressure ulcers. Apigenin, a naturally occurring flavonoid abundantly present in vegetables and fruits, exhibits remarkable efficacy in glycemic control, blood lipid regulation, and antioxidation[20, 21]. The recurrence of inflammation is the primary obstacle in healing diabetic pressure ulcers. Research has demonstrated that apigenin can safeguard the regeneration of β cells by inhibiting the inflammatory pathway[22-24], thereby suggesting a potential significant role for apigenin in facilitating pressure ulcer healing[25-27]. Zizhu ointment (ZZO) is a traditional Chinese medicine preparation extensively utilized in the long-term clinical practice for treating diabetic pressure ulcer healing. Wang et al. [28]conducted network analysis and experimental evaluation of ZZO's efficacy in promoting pressure sore healing, revealing its ability to activate the PI3K/AKT pathway, induce M2 polarization, and subsequently stimulate secretion of IL-4, IL10, and VEGF. These mechanisms ultimately facilitate collagen deposition and angiogenesis, thereby facilitating wound healing. However, due to the poor water solubility and low utilization rate characteristic of Chinese medicine, it may impede skin stratum corneum absorption.

4. Nano-TCM and Its Mechanisms in Treating DPUs

Nanotechnology is the scientific study of engineered materials and systems at the molecular scal[29], which has gained significant traction in the medical field in recent years. Nano Chinese medicine refers to the utilization of nanotechnology for preparing active components, compound preparations, and original drugs derived from traditional Chinese medicine. It should be noted that nano Chinese medicine is not a novel drug per se but rather an outcome of applying nanotechnology to traditional Chinese medicine.

4.1 The benefits of nano Chinese medicine preparations

4.1.1 The diverse formulations of Chinese medicine

The administration methods of traditional Chinese medicine are primarily oral, which often suffer from drawbacks such as delayed efficacy, limited potency, and low bioavailability. Nanotechnology treatment enables the preparation of traditional Chinese medicine into various dosage forms including gels, sprays, liposomes, etc.

4.1.2 Achieve sustained release of TCM

When traditional Chinese medicine is formulated into nanoparticle preparations, it exhibits a slow-release effect. Sun et al. [30]investigated the sustained-release behavior of ofloxacin/montmorillonite (OFLO/MMT) nanocomposites and observed significant sustained-release behavior in vitro experiments, with distinct release patterns observed in acidic and alkaline environments.

4.1.3 The objective is to achieve targeted drug delivery of TCM

The required TCM nanoparticles were prepared using different polymer materials or surface modifications, based on the distinct distribution of physiological enzymes and bacteria, cell distribution, reticular structure, and lymphatic distribution in various body parts. Gao et al.[31]developed novel turmeric-derived nanovesicles (TNVs) for assessing targeting ability in a glucan sodium sulfate (DSS)-induced mouse model using the IVIS imaging system and evaluating their therapeutic effect on ulcerative colitis (UC). The results demonstrated that TNVs exhibited superior efficacy in reducing inflammatory cytokine expression and promoting M1 to M2 transformation compared to conventional curcumin drugs. Importantly, TNVs ameliorated colitis-related symptoms by restoring the integrity of the intestinal epithelial barrier, modulating the composition and relative abundance of gut microbiota, and reshaping the immune microenvironment.

4.1.4 Enhance the bioavailability of TCM

The application of nanotechnology can address the issue of low solubility in traditional Chinese medicine and enhance the efficacy of traditional Chinese medicine preparations. Cardamosin (CAR) exhibits a broad spectrum of pharmacological activities; however, it is confronted with challenges such as limited water solubility and reduced bioavailability. Liu et al.[32]developed CAR-supported liposomes as nanoparticles and demonstrated their ability to enhance hair growth and expedite the transition of hair follicles into the anagen phase, all while minimizing skin irritation. These findings highlight the potential application prospects of CAR-supported liposome formulations in treating alopecia.

4.2 The research mechanism of nano-Chinese medicine in the treatment of pressure sores

Elevated blood glucose levels pose a significant obstacle to the healing of pressure ulcers. Yang et al. developed cupr-based MOF nanoparticles (HKUST-1 NPs) loaded with metformin hydrochloride and the anti-inflammatory agent curcumin (Cur/MH/HKUST-1 NPs), which were subsequently incorporated into a hydrogel matrix (Cur/MH/HKUST-1@Gel). This approach aimed to modulate the microenvironment within the pressure sore. Interestingly, following 20 days of treatment with Cur/MH/HKUST-1@Gel, diabetic mice exhibited a reduction in blood glucose values by 7.2 mmol L^{-1} when compared to initial levels exceeding 16.7 mmol L^{-1}. Liu et al.[10]fabricated composite microneedles (C/B@APB@Ber-MNs) composed of micronicles prepared from white peony polysaccharide (BSP) with hemostatic properties, carboxymethyl arcanose (CMCS) with antibacterial properties, and loaded with ros sensitive Astragalus Polysaccharide (APS) nanoparticles (APB@Ber). These micronicles were based on the effective ingredients baicalein (Bai) from Scutellaria baicalensis (SB) and berberine (Ber) from Coptis chinensis (CC). The C/B@APB@Ber-MNs were attached to medical tape and inserted into the rat's skin using a homemade applicator. It was observed that the C/B@APB@Ber-MNs group significantly enhanced wound healing by promoting collagen deposition, epithelial regeneration, and immune regulation. The natural antioxidant rosewood stilbene (PTE) has been shown to possess significant therapeutic potential in the treatment of diabetic pressure ulcers. Building upon this, Zhao et al. [33]successfully synthesized poly(3-acrylamidophenyl boric acid-b-pterostilbene) (p[AAPBA-b-PTE]) nanoparticles (NPs). These nanoparticles have demonstrated remarkable efficacy in reducing blood sugar levels, enhancing antioxidant capacity, mitigating inflammatory response, and promoting pressure sore healing. To sum up, nano-Chinese medicine exhibits a profound impact on the management of diabetic pressure ulcers.

5. Challenges and Future Directions

Undoubtedly, nanomedicine presents innovative approaches for disease treatment; however, further extensive research is imperative to translate nanotechnology into clinical practice. Ensuring the safety and biocompatibility of nanocarriers and their degradation products is crucial for clinical application, while further exploration is needed to efficiently target nanocarriers at specific sites. Currently, most literature focuses on rats or mice as research subjects, with a lack of in vivo studies conducted on large mammals. Therefore, it is necessary to develop more precise and convenient delivery methods to enhance clinical convenience. In the future development of nanomedicine, in addition to the aforementioned challenges that necessitate improved solutions, potential advancements can be envisioned: integration of nanomedicine and precision medicine enables customized treatment plans tailored to individual patient needs, thereby optimizing treatment efficacy; synergistic promotion of wound healing can be achieved by combining nanomedicine with other advanced therapies such as stem cell therapy and gene therapy.

6. Conclusion

Nanomedicine in TCM represents a promising avenue for treating DPUs. By enhancing drug delivery, modulating inflammatory responses, reducing oxidative stress, promoting angiogenesis, and exhibiting antimicrobial activity, nanomedicine offers a comprehensive approach to improve wound healing outcomes. However, challenges in scalability, regulatory approval, and toxicity need to be addressed before widespread clinical adoption. Future research should focus on developing multifunctional nanoparticles, exploring personalized medicine, and combining nanomedicine with other advanced therapies to optimize treatment strategies for diabetic patients.

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