International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 10 Issue 12, December 2023, Impact Factor: 7.125

Chitosan-Based Hydrogel with Hemigraphis Colorata and Centella Asiatica: A Novel Approach for Diabetic Ulcer Healing

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ABSTRACT

Chronic diabetic ulcers pose significant challenges in healthcare, demanding innovative wound healing strategies. This research explores a novel proposal of the approach by developing a Chitosan-Based Hydrogel incorporating the healing properties of Hemigraphis Colorata and Centella Asiatica. Chitosan, known for its antibacterial and regenerative properties, forms the hydrogel matrix. Hemigraphis Colorata, enriched with wound healing constituents, and Centella Asiatica, renowned for its role in dermal regeneration, synergistically enhance the hydrogel's therapeutic potential. Insights from Ayurveda practitioners guide the formulation, emphasizing traditional wisdom. Clinical trials are proposed to validate the efficacy of this composite hydrogel in diabetic ulcer healing, presenting a promising alternative to current treatments. The study also underscores the importance of herbal medicine in Kerala-rich in biodiversity, urging collaboration between modern science and traditional Ayurvedic knowledge for holistic healthcare solutions.

Keywords: Centella Asiatica, Chitosan, Hemigraphis Colorata, Hydrogel, Diabetic Ulcer

INTRODUCTION

This paper focuses on the development of an efficient wound dressing for diabetic patients, addressing the limitations of current market offerings such as T-bact Ointment. Prolonged use of T-bact can result in the overgrowth of bacteria or fungi, dryness, itching, and redness at the site of application necessitating a novel approach for diabetic ulcer healing. Our proposed solution involves a Chitosan-Based Hydrogel incorporating Hemigraphis Colorata and Centella Asiatica.

Efficient approaches for skin repair are crucial. Hydrogels, such as chitosan-based ones, are promising wound dressings due to their biocompatibility, biodegradability, and high-water retention. Chitosan, derived from chitin, is a readily available biomaterial with antibacterial and hemostatic properties, making it effective in promoting skin regeneration(1). Hydrogels, 3D structural systems formed by crosslinking hydrophilic polymeric chains, exhibit properties akin to extracellular matrices(2). Advantages of hydrogels in wound healing include superior hydrophilicity for exudate absorption(3) ,maintenance of wound moisture(4), creation of a microbial barrier(3)(5)and low adhesion force to prevent damage during dressing changes. Hydrogels can be broadly categorized as native or synthetic. Native hydrogels, such as chitosan-based ones, utilize polymers like chitosan, sodium alginate, collagen, and sodium hyaluronate(2). Their intrinsic bioactive properties enhance their utility in drug delivery systems. Not only do they play a crucial role in formulating polymeric nanoparticles to improve skin penetration, but they also contribute to the preparation of semisolid bases for cutaneous applications. This dual role enhances viscosity, making these formulations

suitable for effective topical treatment of skin diseases(6). Chitosan, derived from crustacean shells through chitin deacetylation, is a highly studied and attractive hydrogel in wound healing. It exhibits antibacterial (7), anti-inflammatory, antidiabetic(8) and hemostatic properties(9), along with skin regenerative behavior(7). Chitosan also offers superior biocompatibility, biodegradability and economic advantages(10), water-absorption, water-retention, and versatile functionalization through amino and hydroxyl groups on molecular chains(11).

The incorporation of chitosan, known for its anti-diabetic properties, with the whole plant juices of Hemigraphis colorata and Centella asiatica, which possess wound healing and anti-inflammatory properties, is anticipated to yield enhanced results in the treatment of diabetic ulcers. Phytoconstituents of H.Colorata include saponins, flavonoids, terpenoids, coumarins, carbohydrates, carboxylic acids, xanthoproteins, tannins, proteins, alkaloids, steroids, and sterols(12). The in vitro anti-inflammatory assay utilizing the HRBC membrane stabilization method suggests that the anti-inflammatory effects of Hemigraphis colorata extracts may be attributed to the presence of flavonoids, tannins, and phenols(13). The hexane extract of Hemigraphis colorata demonstrated notable antimicrobial efficacy and wound healing properties(14). The application of crude leaf paste from Hemigraphis colorata has been observed to facilitate the process of excisional wound healing(12). In mice, the topical application of Hemigraphis colorata leaf paste accelerates wound contraction and epithelialization; however, oral administration of the substance appears to be ineffective for the same purpose(15). Flavonoids derived from Hemigraphis colorata exhibit noteworthy anti-inflammatory activity, as evidenced by the reduction of the inflammatory response in rats through the administration of acetone extracts of H. Colorata against Carrageenan-induced paw edema(16). The incorporation of Hemigraphis colorata into chitosan hydrogel resulted in enhanced platelet activation, improved blood clotting properties, and increased anti-bacterial activity(17). Centella asiatica extract, administered orally and topically, accelerated rat dermal wound healing by enhancing cellular proliferation, collagen synthesis, maturation, and crosslinking. The extract-treated wounds demonstrated faster epithelialization and higher contraction rates compared to controls, indicating varied positive effects on different phases of wound repair. Madecassol, derived from this plant and comprising madecassic acid, asiatic acid, and Asiaticoside, has demonstrated efficacy in expediting wound healing and grafting. Notably, Asiaticoside plays a pivotal role by enhancing fibroblast proliferation and stimulating the synthesis of the extracellular matrix during the wound healing process(18). Excision wounds were introduced on the rats on third day following the induction of diabetes. The findings of the study suggest that C. asiatica has the potential to enhance wound healing in animals under diabetic conditions(19). This suggested blend of polymer-herbal components emerges as a hopeful and pertinent substitute for the management of diabetic ulcers.

METHODOLOGY

A. Interview with Ayurveda Doctor

The study initiated with a comprehensive interview with an Ayurveda doctor specializing in diabetic wound management. The purpose of the interview was to gather insights into traditional wound healing practices, specifically focusing on the use of Hemigraphis Colorata and Centella Asiatica in Ayurvedic medicine. The doctor provided valuable information on the historical context, preparation methods, and observed efficacy of these herbal components in diabetic ulcer healing. This qualitative data played a pivotal role in guiding the formulation of the Chitosan-Based Hydrogel.

B. Literature Review

The literature review was conducted to consolidate existing knowledge on wound healing, hydrogels, and the individual properties of Chitosan, Hemigraphis Colorata, and Centella Asiatica. Two main methodologies were identified in the literature: (a) the formulation and application of chitosan-based hydrogels for wound healing, and (b) the traditional use of Hemigraphis Colorata and Centella Asiatica in various medicinal applications, with a focus on their potential in diabetic ulcer management. This review provided a scientific foundation for the integration of these components into a novel wound dressing.

INTERVIEW

A. Interview with Ayurveda Doctor

In our quest to integrate traditional wisdom with modern scientific advancements in wound healing, we sought insights from an experienced Ayurveda practitioner. With over five years of expertise, the doctor specializes in treating a spectrum of diseases, emphasizing infectious and lifestyle disorders, notably diabetes and degenerative ailments.

Experience in Ayurveda field: Doctor explained her experience in the field and provided a brief summary of the diseases she treats. She said that "I have been practicing Ayurveda for more than 5 years, and various diseases, including infectious and lifestyle disorders, have been treated by me. Mainly, a focus is maintained on lifestyle disorders such as diabetes and degenerative diseases".

Medicinal and therapeutic properties: "Hemigraphis Colorata, belonging to the Acanthaceae family, is known by various names like Aluminium plant and Waffle plant in India. It's recognized for its notable attributes such as wound healing, antidiabetic properties, and antibacterial activities. In Kerala, the plant is popular in the name 'murikootti' or 'murianpacha' because of its incredible potency to heal wounds. Similarly, Centella Asiatica, commonly referred to as Indian Pennywort and classified under the Apiaceae family, holds a significant place in Ayurveda. It's often acknowledged as a "Brain food" in India and is traditionally utilized for treating skin problems, promoting wound healing, acting as a nervine tonic, and improving memory. Additionally, in the treatment of dropsy, it serves as an important herb. According to Ayurveda, it is kapha – pitha hara. Interestingly, in some tribal regions, this plant is even used as a vegetable. Personally, I also use Hemigraphis for simple wounds".

Dosage and formulations: "The dosages often depend on the other ingredients in the formulation and the type of formulation being prepared. For external applications, the leaf juice of Hemigraphis is commonly used by squeezing the leaf, and in that case, the dosage isn't particularly significant. Now, when it comes to Centella Asiatica, it's frequently used in many Ayurvedic brain tonics, usually combined with other ingredients. So, the dosage can vary based on the specific formulation and its intended purpose".

Common formulations: "In Ayurveda, there are quite a few formulations where Centella (Mandooka Parni), takes center stage. It's a key ingredient, known for its role as a Medhya Rasayana in treating mental ailments and boosting immunity. However, when it comes to Hemigraphis, it's a bit disappointing to note that formulations containing this herb are relatively rare. Surprisingly, its remarkable properties, especially in wound healing, aren't fully utilized in Ayurveda. What's intriguing is that there are no formulations that include both of these herbs together."

Current importance and research: "In my practice, I've used Hemigraphis Colorata for a couple of patients dealing with simple wounds. I observed a noticeable reduction in bleeding and improved wound healing, particularly when I used the squeezed leaf juice. However, due to the inconvenience of using the leaf juice regularly and the lack of proper formulations, I haven't explored its use extensively. Now, when it comes to Centella Asiatica, I often recommend it in my clinic during counseling sessions, especially for school students dealing with academic stress. Interestingly, though, the anti-diabetic and wound healing properties of Centella aren't widely utilized, neither by me nor extensively in Ayurveda. From what I know, there are some research papers exploring the unique properties of Ayurveda, but the practical implementations aren't widespread. I believe more research and studies are essential to fully understand and leverage the potential of these herbs."

Possibilities of pure herbal treatments in Kerala: "Kerala is a great place for making medicines from plants. With lots of different plants around, especially some that you can only find here, we can create new and natural ways to help people with their health. Kerala is also good at studying and trying out these new ideas. So, using only herbs for making medicines has a lot of possibilities here, and it can bring new and better ways to treat health issues."

B. Findings from the interview

- Collaborate with Ayurveda Experts: Collaborate with experienced Ayurveda practitioners in Kerala to explore the diverse flora for potential herbal treatments.
- Incorporate Hemigraphis Colorata in Wound Healing: Further research and development could focus on incorporating Hemigraphis Colorata into Ayurvedic wound healing formulations, considering its proven efficacy in reducing bleeding and enhancing wound healing.
- Optimize Usage of Centella Asiatica: Investigate ways to optimize the usage of Centella Asiatica in Ayurvedic brain tonics and stress management formulations, potentially unlocking its anti-diabetic and wound healing properties.
- Formulation Exploration: Consider exploring novel formulations that combine Hemigraphis Colorata and Centella Asiatica, potentially leveraging the synergistic effects of these herbs for enhanced therapeutic outcomes.

- Research on Traditional Formulations: Engage in research on traditional formulations in Kerala that may incorporate these herbs, aiming to revive or adapt them for modern applications.
- Conduct Clinical Trials: Plan and conduct clinical trials to validate the effectiveness of herbal treatments, especially focusing on diabetic ulcer healing using the proposed Chitosan-Based Hydrogel with Hemigraphis Colorata and Centella Asiatica.
- Promote Herbal Medicine Awareness: Collaborate with healthcare professionals and community leaders to raise awareness about the potential of herbal treatments in Kerala, fostering a greater understanding and acceptance of Ayurvedic practices.

PREPARATION OF HEMIGRAPHIS-CHITOSAN–CENTELLA COMPOSITE HYDROGEL

Chitosan is dissolved in 1% acetic acid through constant stirring, creating a solution that can be neutralized with NaOH solution. Fresh crude extract from Hemigraphis and Centella Asiatica leaves is collected, lyophilized, and then added to the Chitosan solution, ensuring uniform mixing through stirring(17). The resulting homogeneous mixture is cast into a mold and subjected to a freeze-thaw cycle, alternating between freezing at -18 °C for 8 hours and thawing at room temperature. This cycle is can be repeated up to approximately 5 times, ultimately yielding the desired Hemigraphis-Chitosan–Centella composite hydrogel wound dressing(4).

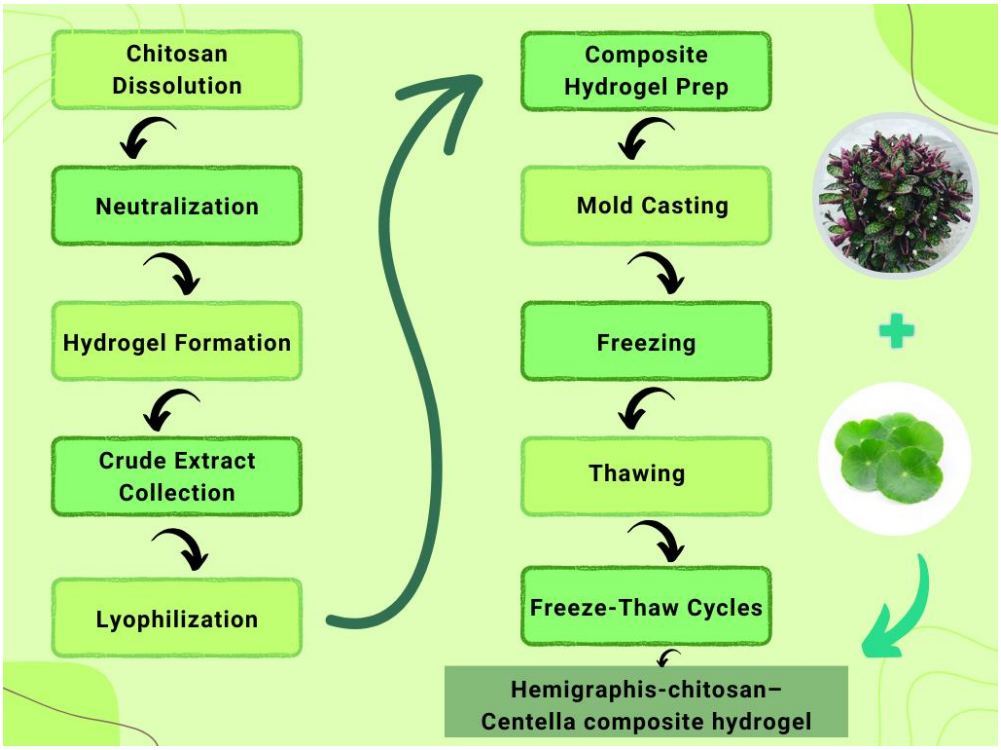

Figure 1. Flow-diagram of procedure of hydrogel preparation

CONCLUSION

The proposed research introduces a novel and promising approach to diabetic ulcer healing through the development of a Chitosan-Based Hydrogel incorporating Hemigraphis Colorata and Centella Asiatica. The synergistic combination of Chitosan's antibacterial and regenerative properties with the wound healing and anti-inflammatory attributes of Hemigraphis Colorata and Centella Asiatica presents a unique solution to address the limitations of current diabetic wound dressings. Insights from an Ayurveda doctor specializing in diabetic wound management provided valuable traditional knowledge, guiding the formulation of the hydrogel. The interview emphasized the historical significance and therapeutic properties of Hemigraphis Colorata and Centella Asiatica, urging further exploration and optimization of their usage in Ayurvedic formulations. The methodology involved a comprehensive literature review, consolidating scientific evidence supporting the integration of these components into an efficient wound dressing. The formulation process combined Chitosan with fresh extracts of Hemigraphis Colorata and Centella Asiatica, resulting in a composite hydrogel with potential applications in diabetic ulcer management. Findings from the Ayurveda expert interview

highlighted the need for collaboration with Ayurveda practitioners, exploration of Hemigraphis Colorata in wound healing, optimization of Centella Asiatica usage, formulation exploration, research on traditional formulations, and the importance of clinical trials to validate herbal treatments.

The proposed Chitosan-Based Hydrogel with Hemigraphis Colorata and Centella Asiatica holds promise as an alternative to current market offerings, addressing the challenges associated with prolonged use of existing treatments. This research not only contributes to the field of wound healing but also advocates for the integration of traditional herbal wisdom with modern scientific advancements, promoting awareness and acceptance of herbal medicine in diabetic ulcer management.

LIMITATIONS & FUTURE ASPECTS

A. Limitations

The study's limitations stem from its predominantly theoretical nature. The proposed Chitosan-Based Hydrogel, incorporating Hemigraphis Colorata and Centella Asiatica, lacks practical synthesis and laboratory testing, thus necessitating experimental validation.

B. Future Aspects

- Laboratory Validation and Optimization: Conduct rigorous laboratory experiments to synthesize and validate the proposed Chitosan-Based Hydrogel with Hemigraphis Colorata and Centella Asiatica. Optimize the formulation for enhanced efficacy in diabetic ulcer healing.
- Clinical Trials for Efficacy: Initiate well-designed clinical trials to evaluate the effectiveness of the composite hydrogel on actual diabetic ulcer cases. Gather empirical evidence to support its therapeutic benefits and compare its performance against existing treatments.
- Dosage Determination: Undertake systematic studies to determine optimal dosages for the individual components and their synergistic combination in the hydrogel. Precise dosage information is crucial for ensuring therapeutic efficacy and minimizing potential side effects.
- Multi-Expert Collaboration: Expand collaboration with multiple Ayurveda practitioners to incorporate diverse perspectives and experiences in the formulation process. This will contribute to a more holistic understanding of the herbal components and their potential applications.
- Exploration of Additional Herbal Synergies: Investigate other herbal combinations that may complement the proposed hydrogel. Explore synergies with additional plant extracts to enhance the wound healing properties and overall therapeutic potential.
- Community Awareness and Acceptance: Launch awareness campaigns targeting healthcare professionals and community leaders to promote acceptance and understanding of herbal medicine in diabetic ulcer management. Foster collaborations between traditional Ayurvedic practices and modern healthcare for comprehensive solutions.

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