

Chitosan and Liposomes Nanoparticles Encapsulated Cinnamon Extract: Antiproteolytic Activity and Wound Healing Efficiency of Diabetic Rats
Running Head: Chitosan vs Liposomes Nanoparticles as Drug Delivery Carriers

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ABSTRACT

*Diabetic foot infection is a major concern between diabetic communities as it is increasing rapidly with more virulent organisms. These virulent organisms include the flesh and bone eating bacteria which produce proteolytic enzymes in order to hydrolyze the skin, flesh and bone. When the infection spreads, physicians lean to amputation followed by a long term of broad spectrum antibiotics. Even after complete eradication of bacteria, their proteolytic enzymes remain in the blood circulation which leads to prior amputation. Thirty three bacterial isolates were isolated from foot ulcers of diabetic patients. The most prevalent isolates were *Proteus mirabilis* and *Pseudomonas aeruginosa*. The selected bacterial isolates were tested for protease production on different protein sources including collagen (the most abundant compound in human's connective tissue). Eighteen herbal extracts were examined for their effect against the proteolytic activity of the selected*

isolates. Cinnamon ethanolic extract was the most effective anti-proteolytic agent. Chitosan and liposomes nanoparticles loaded with cinnamon ethanolic extract were prepared and their physicochemical characteristics were evaluated. For assessment of wound healing efficiency, gel of both Chitosan and liposomes nanoparticles loaded with cinnamon ethanolic extract was tested in wounded diabetic rats and it was found that liposomes/cinnamon gel was more effective as wound healing remedy.

Keywords: Diabetic foot, Proteases, Amputation, Cinnamon, Chitosan nanoparticles, Liposomes

INTRODUCTION

Complications of a wound associated with bacterial infection delays healing and in some cases it can be fatal. In diabetic foot patient, infected wound is a major concern because it can lead to hospitalization and amputation as the bacteria get more virulent by time. Foot ulcers infection is commonly severe complication in diabetes. The clinical diagnosis of infected ulcer are based on local signs and symptoms include purulent secretion, redness, warmth, swelling, pain, offensive odor and delayed healing (Lepäntalo et al., 2011).

Diabetic foot infections (DFI) are mainly polymicrobial, the variability of bacterial virulence factors and the level of host resistance must also be taken into account (Al Wahbi, 2018). One of the bacterial virulence factors is the extracellular proteolytic enzymes which have a key role in host colonization by assisting the pathogen spread into host tissues. They also improve the pathogen survival and growth by increasing (a) the availability of amino acids and (b) toxins diffusion (Dunyach-Remy et al., 2016). In diabetic and arterial foot lesions, Gram-positive aerobic cocci grow in 59% of cultures (24% are colonized by *S. aureus*) while Gram-negative aerobes grow in 35% of cultures (frequently *Escherichia coli* and *Proteus mirabilis*) (John and Sharkey, 2018).

The Phytochemical compounds presented in plants' secondary metabolites are gaining enormous attention in the human health care researches especially as new potent antimicrobial agents. However, protease inhibitors (PIs) are still not fully explored which protect the plant itself against diseases, insects, pests, and herbivores (Srikanth and Chen, 2016). Cinnamon has been used as spice for a long time. Cinnamon can be found as True or Ceylon cinnamon (*Cinnamomum verum* and *C. zeylanicum*) and cassia cinnamon (*C. aromaticum* and *C. burmannii*). Cinnamon has been used as a dietary supplement, antioxidant, antiinflammation, and presently discovered antihyperlipidemia and antiobesity effect properties (Tuzcu et al., 2017). However the anti-proteolytic activity of cinnamon extract wasn't yet fully explored which will be covered in the present manuscript.