BROMELAIN-BASED ENZYMATIC DEBRIDEMENT: MECHANISM OF ACTION IN WOUND HEALING PROCESSES - A LITERATURE REVIEW

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Overview

INTRODUCTION

Chronic hard-to-heal wounds, such as diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), and pressure ulcers, pose significant safety risks, burdens on patients, and challenges to healthcare systems worldwide. A literature review was performed to assesses the mechanism of action and clinical effects of Bromelain-based Enzymatic Debridement (BBD) in the context of acute and chronic wound care. Un-published mechanistic studies with BBD are described.

BROMELAIN BASED DEBRIDEMENT (BBD)

- Investigational biological product in ongoing Phase III clinical trial in VLU
- Mixture of proteolytic enzymes enriched with bromelain, derived from the stem of pineapple plant
- Same active ingredient as NexoBrid®, FDA/EMA approved for eschar removal in burns
- Phase 2 trials (VLU, DFU, traumatic ulcers) showed superiority over placebo hydrogel & non-surgical standard of care 1,2 in debridement of non-viable tissue, and promotion of granulation tissue in patients with chronic wounds

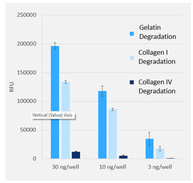
METHODS

A thorough literature review was conducted on bromelain's mechanism of action as well as clinical and pre-clinical studies conducted with BBD, using PubMed and Google Scholar databases, covering articles published between November 1992 and December 2023. 94 articles were reviewed and 70 utilized as references.
Additionally, preliminary in-vitro mechanistic studies with BBD testing its affinity to extracellular matrix components were conducted.

Results

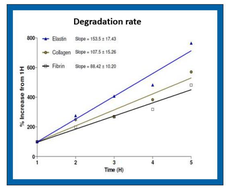
SELECTIVE REMOVAL OF DENATURED COLLAGEN

- Eschar in burn wounds consists primarily of gelatin, a denatured form of collagen
- In chronic wounds, MMPs degrade intact collagen, leading to denatured, non-functional collagen that impairs wound healing
- BBD degrades gelatin at a much faster rate than collagen type I and IV



MULTI-TARGETED PROTEOLYTIC ACTIVITY

- ECM proteins e.g., fibrin, collagen, elastin are over-secreted in chronic wounds
- Accumulation of these degraded proteins prevents the progression to normal healing
- BBD enzymes degrade over-secreted ECM proteins and facilitate the removal of various denatured proteins from the wound bed



Shoham et al. 2021; Wound Rep Reg

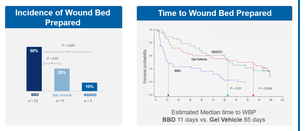
PROMOTION OF GRANULATION TISSUE

Essential role of granulation tissue:
- Angiogenesis
- Induce collagen deposition in the wound bed
- Enhance fibroblasts proliferation and migration
- Promote wound contraction
- Protects against infection
- Promotes epithelial cells to migration
- Reduces inflammation

Gurtner *Nature* 2008; Martin *British Journal of Dermatology* 2015; Darby *Clinical, Cosmetic and Investigational Dermatology* 2014; Diegelmann *Frontiers in Bioscience* 2004

Preparation of wound Bed (complete debridement and complete cover with granulation tissue), to facilitate healing

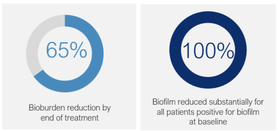
- TGF-β ↑ – inducing the formation and granulation tissue and differentiation of myofibroblasts
- VEGF ↑ - promote vascularization
- IL-6 ↑ - Regulation of myofibroblasts



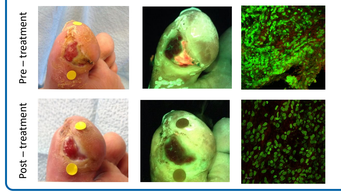
Shoham et al. *eClinicalMedicine (Lancet group)* 2024

REDUCTION OF BIOBURDEN AND BIOFILM

- Reduces bioburden
- Removes biofilm
- Reduces pro-inflammatory cytokines: - IL-1β, IL-6, TNF-α, PGE-2, NF-κB
- Release of nitric oxide (NO) from endothelial cells



Snyder et al. 2023; Wounds



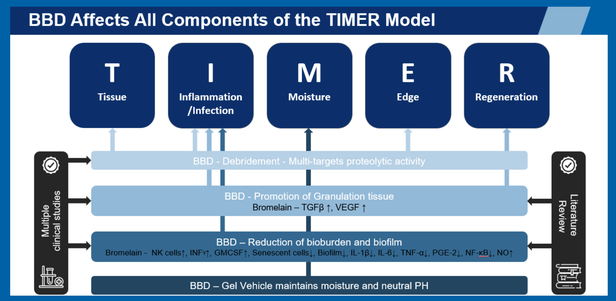
Left
Wound bed pre- and post-treatment (5 applications).

Middle
Red fluorescing bacteria (MolecuLight®).

Right
biopsies showing thick continuous film before and single organism after

Snyder et al. 2023; Wounds

Summary and Conclusions



BBD, a mixture of proteolytic enzymes derived from the pineapple stem, demonstrates multifaceted actions, potentially beneficial in wound healing:

- Selectivity - greater affinity towards denatured collagen than native collagen
- Multi-targeted proteolytic activity - degrades over-secreted extracellular matrix proteins (e.g., fibrin, elastin).
- Anti-bacterial / Anti-inflammatory - reduction of bioburden and biofilm and reduces inflammation
- Promotes granulation tissue
- Maintains moisture balance

CONCLUSION

The mechanistic insights provided in this review underscore the potential of BBD as a novel standard in chronic wound care, warranting further clinical studies in various wound types