# Bromelain-Based Enzymatic Debridement: Mechanism of Action in the Wound Environment. A Literature Review

Robert Snyder, DPM, MSc, MBA
Timothy Hoffmeister, BS
Joey Karim Ead, DPM, MS
Anwar Nass, MBS, BS
Ety Klinger, PhD, MBA
Keren David-Zarbiv, MSc, BS
Yael Kats-Levy, PhD
Aya Ben Yaakov, PhD, MSc, BS

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## Abstract

**Background.** Chronic hard-to-heal wounds, such as diabetic foot ulcers, venous leg ulcers, and pressure ulcers, present significant safety concerns, patient burdens, and challenges to health care systems globally. **Objective.** To review the mechanism of action and clinical function of bromelain-based enzymatic debridement (BBD) in the context of wound care, focusing on the mechanism of action of BBD and its formulation for chronic wounds in particular. **Methods.** A literature review was conducted to assess both bromelain's mechanism of action as well as clinical and preclinical studies on the use of BBD, searching the PubMed and Google Scholar databases for articles published between November 1992 and July 2024. **Results.** The literature review shows that BBD, a mixture of proteolytic enzymes derived from the pineapple plant, demonstrates multifaceted actions beneficial to wound healing. It selectively targets devitalized tissue, inhibits bacterial biofilm formation, promotes granulation tissue formation, and maintains moisture balance, thus facilitating a conducive wound microenvironment. Clinical studies and in vivo experiments support the efficacy of BBD in expediting wound debridement, in the formation of granulation tissue, and in reducing bioburden. **Conclusion.** The mechanistic insights presented in this review underscore the potential of BBD as a novel standard in chronic wound care that warrants further exploration and clinical validation across diverse wound classifications.

**Abbreviations:** BBD, bromelain-based enzymatic debridement; COX-2, cyclooxygenase 2; DFU, diabetic foot ulcer; ECM, extracellular matrix; EPS, extracellular polymeric substance; FDA, US Food and Drug Administration; GV, gel vehicle; IL, interleukin; INF-γ, interferon gamma; MF, myofibroblast; NF-κB, nuclear factor-κB; NK, natural killer; NSSOC, nonsurgical SOC; PGE-2, prostaglandin E2; ROS, reactive oxygen species; SOC, standard of care; TBSA, total body surface area; TGF-β, transforming growth factor β; TIME, devitalized tissue, infection/inflammation, moisture balance, and edge preparation; TNF-α, tumor necrosis factor α; VLU, venous leg ulcer; WBP, wound bed preparation.

## Background

Chronic hard-to-heal wounds, such as DFUs, VLUs, and pressure ulcers, are a substantial burden on health care systems and patients worldwide. In addition, acute posttraumatic and surgical wounds may stall and become recalcitrant, hard-to-heal chronic wounds. These wounds can lead to severe medical sequelae, prolonged suffering, reduced quality of life, and significant health care costs. The effect is not only on the individual level but also on a broader scale, including the patient's family and close environment, as well as health care resources and economics.[1,2]

WBP is an important paradigm used to assess and manage chronic wounds.[3] Within this WBP paradigm, wounds are broken down into their primary components: devitalized tissue, infection/inflammation, moisture balance, and edge preparation, or TIME.[4,5] As each component is addressed, the prolonged inflammatory phase is able to transition into the proliferative and remodeling phases of healing. The dynamic nature of wound healing becomes more pronounced in chronic wounds due to complicating factors, including ischemia, extensive fungal and bacterial colonization, neuropathy, swelling, and the accumulation of exudates and necrotic tissue over the wound bed.[6-9]

Debridement, defined as the removal of all nonviable, infected, and foreign material from a wound bed, has proven to play an integral role in the treatment of various wounds, such as burns, DFUs, arterial ulcers, VLUs, and pressure ulcers.[10,11] Available wound debridement methods are tailored to specific patient needs and wound characteristics, including surgical, sharp, mechanical, autolytic, biologic, and enzymatic debridement. The choice of debridement method depends on matching the available method to clinical factors such as wound type, wound size, and patient-specific considerations.

Enzymatic debridement is a targeted approach to chronic wound healing that utilizes topical agents containing specific enzymes to selectively break down necrotic tissue without harming native healthy structures. It has proved to be effective both on its own and in conjunction with other debridement modalities and is generally less invasive and less painful than mechanical or surgical debridement methods.[12,13] Enzymatic debridement is particularly useful when traditional surgical debridement may be challenging or not well-tolerated by the patient.

Currently, collagenase is the only FDA-approved enzymatic debridement product indicated for treating chronic wounds and severe burns; however, its slow debridement capabilities have created a need for additional, more expedient options.[14] This need has prompted the development of a concentrated mixture of proteolytic enzymes enriched in bromelain derived from the stem of the pineapple plant (BBD) to allow for more rapid debridement while maintaining selectivity for devitalized tissue.

Stem bromelain is a mixture of different enzymes, such as thiol endopeptidases, phosphatases, glucosidases, and protease inhibitors. In vitro and in vivo studies demonstrate that bromelain exhibits various activities, such as proteolytic activity, anti-inflammatory activity, apoptotic activity, and anti-tumorigenic activity.[12]

Two different formulations of BBD, EscharEx (MediWound Ltd; hereinafter ESX) and NexoBrid (MediWound Ltd; hereinafter NXB), show promise in debridement and preparation of the wound bed for subsequent treatments to heal chronic wounds (VLU and DFU) and acute wounds (thermal burns), respectively. ESX is a sterile, lyophilized powder containing a concentrated mixture of proteolytic enzymes enriched in bromelain blended with excipients to form a low bioburden dosage strength of 5.0%. NXB is a lyophilized bromelain powder and GV for cutaneous use in burns. After mixing the powder with the GV, each gram of the prepared product contains 0.09 g of partially purified bromelain. Two grams of NXB sterile powder are mixed in 20 g of sterile GV (ratio of 1:10). NXB gel is applied to a burn wound at a dose of 2 g mixed with 20 g sterile GV per 1% TBSA for 4 hours.[15]

The aim of this literature review is to describe the various aspects of BBD activities in WBP for chronic wounds.

## Methods

Four reviewers (R.S., T.H., J.K.E., and A.N.) performed a literature review using the following keywords and search terms: "bromelain," "wound debridement," "wound bed preparation," "granulation tissue," "inflammation," "infection," and "biofilm." In total, 94 articles were reviewed, and 70 were ultimately used as references. The selected journal articles, which were found by searching PubMed and Google Scholar, were published between November 1992 and July 2024.

## Results

Results of the identified studies were analyzed to assess whether the treatment of chronic wounds with BBD addresses major components of WBP (**Figure 1**).

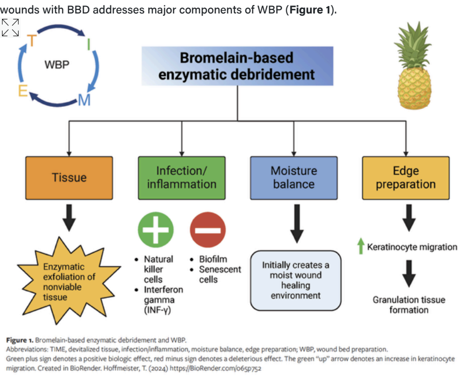


**Figure 1.** Bromelain-based enzymatic debridement and WBP.
Abbreviations: TIME, devitalized tissue, infection/inflammation, moisture balance, edge preparation; WBP, wound bed preparation. Green plus sign denotes a positive biologic effect; red minus sign denotes a deleterious effect. The green "up" arrow denotes an increase in keratinocyte migration. Created in BioRender. Hoffmeister, T. (2024) https://BioRender.com/o6g2752

### Debridement of devitalized tissue

Removing devitalized tissue, such as eschar and slough, is paramount for initiating and continuing wound healing. Devitalized tissue not only serves as a physical barrier to healing but also stimulates the production of various enzymes that destroy the so-called building blocks of wound healing, including growth factors and chemoattractants.[10] Devitalized tissue also creates an environment ideal for colonization and infection with various microorganisms, thereby worsening the already poor healing environment.[16]

A concentrated mixture of proteolytic enzymes enriched in bromelain has many functions that help promote a more favorable wound healing environment (**Table**). The most prominent role of bromelain is its ability to selectively and rapidly digest necrotic tissue, thus targeting and hydrolyzing (ie, breaking down via a chemical reaction with water) its primary structural constituents, including fibrin, elastin, and collagen.[17] This has been demonstrated in numerous clinical and preclinical studies focused on BBD drug products such as NXB in the treatment of acute thermal burn wounds and ESX in the treatment of DFUs and VLUs.[18–22]

| **Table.** Beneficial Properties of Bromelain-Based Enzymatic Debridement |
|---|
| Selective mechanism of action |
| Proteolysis |
| Anti-inflammatory effects |
| Facilitation of autolytic debridement |
| Promotion of granulation tissue formation |
| Potential antibacterial effects |

BBD has numerous enzymatic abilities because it is a complex mixture of many enzymes, such as thiol endopeptidases, glucosidase, peroxidase, phosphatase, cellulase, and protease inhibitors, which undoubtedly contributes to its wide range of therapeutic applications, including its ability to quickly and effectively remove devitalized tissue.[12,23] BBD has a broad substrate specificity, which contributes to BBD's ability to successfully and rapidly digest numerous types of collagen and other proteins, such as gelatin, fibrin, and elastin, while remaining selective for denatured proteins and devitalized tissue.[24–26]

### Results of BBD in the treatment of burn wounds

In a multicenter prospective phase 3 randomized controlled trial by Shoham et al,[27] adult patients with deep burns covering 3% to 30% of TBSA were randomized to BBD (n = 75), SOC (n = 75), or placebo control GV (n = 25). The results revealed that patients treated with BBD had less need for surgical eschar removal than those treated with the SOC (4% and 72%, respectively). Furthermore, 93.3% of patients treated with BBD achieved complete eschar removal within 4 hours compared with only 4% of patients in the GV group ($P$ < .0001). The BBD group had better cosmetic and functional results than the SOC group 12 months after treatment, as well as lower levels of general anesthesia and less blood loss (14 mL in the BBD group vs. 815 mL in the SOC group).

### Results of BBD in the treatment of chronic wounds

Since 2018, BBD (ie, ESX) has demonstrated success in treating chronic wounds.[28–30] In a prospective, randomized, multicenter, placebo-controlled trial conducted across 20 medical centers and clinics in the United States, Switzerland, and Israel, the efficacy of BBD was compared with that of GV (placebo) and NSSOC using various dressings such as collagenase and hydrogel.[30] The study aimed to assess the incidence of complete debridement in patients with VLUs. The results showed that 63% of those treated with BBD achieved complete debridement after 8 daily treatments (29 of 46 patients), compared with 30.2% (13 of 43 patients) in the GV group ($P$ = .004) and 13.3% (4 of 30 patients) in the NSSOC group ($P$ < .001).

In a prospective randomized controlled trial of 73 patients, Shoham et al[28] demonstrated the efficacy of ESX as a BBD agent on DFUs, VLUs, and postoperative and posttraumatic hard-to-heal wounds. The BBD group exhibited a significantly higher incidence of complete debridement compared with the GV group (55% vs. 29%; $P$ = .047).

### Time to debridement using BBD

Time to complete debridement is an important aspect of wound healing and, as mentioned above, is one of the drawbacks of collagenase, the current standard in enzymatic debridement, resulting in longer debridement time. This problem is overcome with BBD; earlier and faster debridement is the most frequently mentioned advantage of BBD agents.[31]

The results of a multicenter randomized controlled trial comparing BBD with NSSOC and GV in the treatment of VLUs were originally reported at the Symposium on Advanced Wound Care Fall 2022, held October 13 through 16, 2022, in Las Vegas, Nevada and subsequently published in 2024 by Shoham et al.[27,32] Researchers revealed that the time to complete debridement was only 9 days in the BBD group compared with 59 days in the NSSOC group ($P$ = .016). The results from the phase 3 DETECT study (deep partial- and full-thickness burns) exhibited a faster average time to complete eschar removal with BBD compared with SOC (1 day and 3.8 days, respectively).[27]

In a single-center controlled trial by Schulz et al,[22] 40 patients with deep dermal and full-thickness hand burns were treated with either BBD or surgical debridement. BBD was superior to surgical debridement, with BBD significantly reducing both the time to complete debridement (0.95 days and 7.75 days, respectively) and the number of treatments needed for complete debridement (1.05 and 1.45, respectively) while at the same time reducing the need for autografting, reducing time to complete healing, and improving scar quality. Rosenberg et al[21] conducted a multicenter, open-label, randomized controlled clinical trial of 182 patients with deep burn who were randomly assigned to either BBD nonsurgical treatment or SOC surgical or nonsurgical debridement. The time to complete debridement from injury was reduced from a mean 8.7 days in the SOC group to 2.2 days in the BBD group, and BBD also reduced the need for surgery and autografting.

Overall, BBD allows for a fast and effective minimally invasive treatment approach with similar, and in some cases better, results than SOC, including collagenase, often reducing the need for subsequent surgery or grafting.

### Effect of BBD on bacteria and biofilm

Colonization and infection with numerous microorganisms is common in chronic wounds, leading to delayed healing.[33] The literature indicates that approximately 60% of chronic wounds are believed to be infected; therefore, removing nonviable tissue remains critical.[34] Bacteria delay wound healing through the secretion of endotoxins and exotoxins.[35] When infection occurs, bacteria continue to produce toxins and destructive enzymes, causing the release of ROS, and together with the inflammation that is a part of this process, these substances consume valuable nutrients needed for the survival of healthy tissue.[11,36] This commonly results in further tissue death and, thus, a more susceptible environment for additional colonization. With additional colonization comes the formation of biofilm, a common barrier to normal wound healing because it impairs the formation of new tissue (including granulation tissue) and reduces susceptibility to antimicrobial agents and normal host defense via its EPS component.[36,37]

Snyder et al[38] tested the ability of BBD to reduce biofilm and promote complete debridement in patients with DFUs and VLUs. In an open-label, proof-of-concept study of 12 patients, biofilm and bacterial load were assessed using punch biopsy and fluorescence imaging. The study results revealed that all patients initially found to be positive for biofilm at baseline before treatment with BBD showed a marked decrease in biofilm, with the biofilm reduced to either a single microorganism or an undetectable level. The mean biofilm score was 2.2 before treatment and 1 after treatment, indicating the presence of only individual organisms following an average of 6 applications of BBD. One subject had a pretreatment biofilm score of 5, indicating the presence of a thick, continuous film of microorganisms. The biofilm score was 1 after the final treatment. In addition, wound assessment using MolecuLight i:X (MolecuLight), a wound imaging device that allows clinicians to visualize bacteria quickly, safely, and easily, showed that the average area of red fluorescence, representing bacterial load, was 1.09 $cm^2$ before treatment and 0.39 $cm^2$ after treatment.

BBD's ability to reduce biofilm was further demonstrated in a study by Watters et al,[39] in which a *Staphylococcus aureus* biofilm model was created to mimic wound-like conditions. The biofilm was then subjected to bromelain, which resulted in a 98% reduction in biofilm mass confirmed through scanning electron microscopy, demonstrating the detachment of biofilm EPS and bacteria from growth surfaces. Overall, the results indicated that enzymes such as bromelain may be an effective means of eradicating biofilms and a promising strategy to improve the treatment of multidrug-resistant bacterial infections.

A literature review published in 2017 revealed that the antibiofilm abilities and the antimicrobial action of BBD are due to the enzymatic properties of bromelain. In a study by Ataide et al,[40] the antimicrobial action of bromelain against *Escherichia coli, Pseudomonas aureoginosa*, and *S. aureus* was assessed, and it was concluded that this antimicrobial action of bromelain was related to bromelain's enzymatic action, thus demonstrating the efficacy of bromelain in the inhibition of both gram-negative and gram-positive bacteria.

Another beneficial aspect of bromelain's antimicrobial action is its ability to function in a wide pH range of 4.5 to 9.5. The presence of bacteria is known to affect wound pH, potentially altering the efficacy of certain treatments.[41,42] Furthermore, the BBD formulation for chronic wounds (ESX) contains phosphate buffer with a strong buffer capacity, which maintains a neutral wound bed pH during application.[43]

### Antioxidant properties of bromelain

Besides effectively digesting protein and removing eschar from wounds, BBD may exhibit antioxidant action, as bromelain has been shown to combat further tissue damage and death. These antioxidant actions include lipid peroxidation inhibition and free radical scavenging.[44,45] Ataide et al[40] demonstrated bromelain's antioxidant properties, showing it to be statistically similar to glutathione at concentrations of 30 mg/mL and 15 mg/mL. This is especially beneficial because controlling ROS levels has been shown to play a crucial role in normal wound healing.[46] ROS have been associated with antimicrobial action and increased energy for healing; however, if levels become too high, unwanted damage to healthy tissue can occur.[47,48]

### Immunomodulatory effects of bromelain

Bromelain has further demonstrated its ability to aid in fighting infection through its immunomodulatory effects. Specifically, bromelain activates NK cells and INF-γ and increases the production of granulocyte-macrophage colony-stimulating factor.[41] NK cells are crucial in the immune system's defense against senescent cells. Senescence is a cellular state in which cells cease to divide and undergo functional changes, often in response to various stresses or damage. While senescence is a protective mechanism to prevent the proliferation of damaged cells, the accumulation of senescent cells can contribute to aging, replicative senescence, and various age-related diseases, including chronic nonhealing wounds.[49]

### Anti-inflammatory activity

While speculative and not yet studied in the context of chronic wound debridement, the efficacy of the mechanism of action of BBD agents such as ESX could also be due in part to the anti-inflammatory action of bromelain. Numerous factors, including oxidative stress, increased pro-inflammatory mediators, and infection caused by the dysregulation of the normal inflammatory response to tissue damage, often perpetuate the inflammatory stage of healing, leading to recalcitrant, chronic wound formation (**Figure 2**).[50] Bromelain may control the inflammatory response associated with chronic wounds in multiple ways, hypothesizing its ability to function as a topical anti-inflammatory agent. In a study by Badriyya et al,[51] the topical anti-inflammatory action of bromelain was demonstrated in mice using the so-called Granuloma Pouch method. All 3 topically applied concentrations of bromelain gel (0.1%, 0.5%, and 1%) showed anti-inflammatory action by decreasing exudate and total leukocyte numbers.

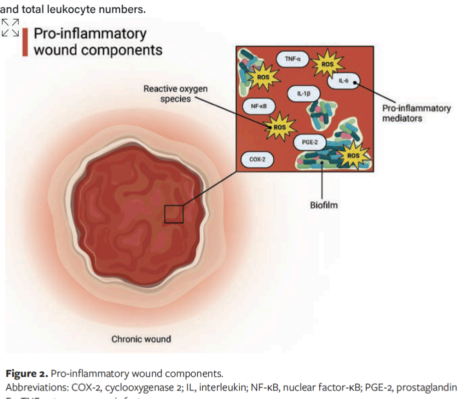


**Figure 2.** Pro-inflammatory wound components.
Abbreviations: COX-2, cyclooxygenase 2; IL, interleukin; NF-κB, nuclear factor-κB; PGE-2, prostaglandin E2; TNF-α, tumor necrosis factor α.
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One way in which bromelain asserts its anti-inflammatory effects is through the regulation of inflammatory mediators. Rathnavelu et al[41] note that bromelain reduces the secretion of IL-1β, IL-6, and TNF-α after an immune response has been initiated, helping to control and prevent prolonged inflammation and, therefore, further tissue destruction.[41] Bromelain also regulates inflammation by reducing the synthesis of PGE-2.[23] This is accomplished by inhibiting COX-2 and blocking the activation of NF-κB.[52,53] This is important because NF-κB has been shown to play a vital role in the induction and persistence of inflammation in multiple conditions, including metabolic diseases such as type 2 diabetes via the IκB kinase/NF-κB pathway.[54,55]

### Moisture balance

Adequate moisture balance, which is usually achieved with numerous dressings, is necessary for successful wound healing. A wound that is too dry or too wet can act as a barrier to healing. For instance, too much moisture in the wound bed, which can be caused by inflammation and infection, can lead to tissue damage such as periwound maceration, impeding healing and further contributing to the destruction of the wound bed.[56] When a wound is too dry, eschar formation commonly occurs, slowing the migration of keratinocytes and subsequent wound reepithelialization.[56,57] Achieving moisture balance is often a result of effectively managing devitalized tissue, infection, and inflammation, all of which are thoroughly addressed by bromelain, as mentioned previously. It is hypothesized that bromelain helps create an environment that encourages adequate moisture balance. BBD is also a hydrogel, further contributing to moisture balance during treatment. After complete debridement is achieved, moisture balance is maintained by other wound management methods.

### Edge preparation

The formation of new, healthy tissue is necessary for wound healing. In wounds that heal via secondary intention, such as chronic wounds and ulcers, granulation tissue fills the wound bed, importing vascular and cellular elements that, after temporarily filling the wound bed, transform into scar tissue that permanently closes the wound. This tissue is characterized histologically by proliferative cells such as fibroblasts, keratinocytes, and endothelial cells.[58] It is hypothesized that the fibrinolytic activity of bromelain may increase blood flow from the wound edge while decreasing TNF-α. Once a healthy wound bed is established, epithelial resurfacing and advancement can begin from the wound edge.[37] This process occurs primarily due to the directed migration of keratinocytes over the wound.[59]

### Promotion of granulation tissue

Granulation tissue consists of newly formed blood vessels, disorganized collagen, and various ECM proteins that fill the wound bed, promoting healing.[58,60] Granulation tissue formation is an essential step in the wound healing process and a key factor contributing to the prevention of chronic wound formation. BBD's ability to encourage the formation of granulation tissue is highlighted in a multicenter randomized controlled trial by Shoham et al[30] in which BBD was used to treat VLUs.

In that study, the incidence of complete debridement and complete granulation was 50% in the BBD group, compared with 25% in the GV group (placebo control) ($P$ = .0108) and 10% in the NSSOC group (various dressings, including collagen and hydrogel) ($P$ = .0002 [post hoc analysis]).[30] Overall, BBD was significantly more effective and faster than NSSOC and placebo GV in forming complete granulation tissue, while being safe and well-tolerated.

BBD's ability to encourage granulation tissue formation may be due to bromelain's effects on growth factors, perfusion, and several important inflammatory mediators. Bromelain has been shown to increase levels of TGF-β, an important growth factor produced by keratinocytes and fibroblasts responsible for inducing the formation of granulation tissue and the differentiation of MFs.[58,61] The increase in TGF-β is also important in the vascularization of granulation tissue, an essential process because poor vascularization often results in delayed healing and the formation of chronic wounds.[62] The role of TGF-β in the vascularization of granulation tissue is due to its upregulation of vascular endothelial growth factor, a protein known to stimulate angiogenesis and positively affect the quality of wound closure and repair.[63,64]

As mentioned previously, IL-6 is an inflammatory mediator regulated by bromelain. IL-6 has also been proven to play an important role in the finalization of wound healing. In a study by Aichele et al[65] showing the in vitro effects of bromelain on MF differentiation, it was demonstrated that, although IL-6 is typically thought of as a trigger for MF differentiation, high levels of IL-6 coincided with decreased MF differentiation following bromelain supplementation. This is important because MF and ECM protein reduction must occur for the normal, nonpathological wound healing process to be complete.[65,66]

### Fibrinolytic properties

The so-called fibrin cuff theory suggests that increased intravascular pressure results in a more profound opening of endothelial pores and, thus, increased interstitial fibrinogen deposition.[67] Further evaluation of the fibrin cuff revealed it to be a complex structure composed of fibrin, type I and III collagen, fibronectin, laminin, tenascin, and trapped leukocytes.[68,69] A fibrin cuff complicates healing, potentially acting as a barrier to the diffusion of oxygen and nutrients, which can contribute to the formation of wounds.[67,70] Although it was initially seen in chronic venous disease, the fibrin cuff is present in other chronic ulcerative diseases, indicating abnormal microcirculation.[69,71]

Bromelain has shown its fibrinolytic properties, not only through its ability to digest fibrin but also through its ability to inhibit its synthesis, thereby reducing serum fibrinogen levels.[12] This supports the hypothesis that bromelain, and therefore BBD, may aid in healing chronic wounds by destroying the fibrin cuff, removing the nutrient barrier, and encouraging healing.

## Discussion

The literature hypothesizes that bromelain, and therefore BBD, has the potential to address the cardinal principles of WBP encapsulated within the TIME framework. BBD shows promise as a valuable tool for treating chronic, difficult-to-heal wounds. Leveraging its intricate enzymatic repertoire, BBD orchestrates the selective degradation and elimination of devitalized tissue components from within the wound bed while sparing surrounding healthy tissue from enzymatic digestion. Furthermore, BBD's enzymatic capabilities have shown proficiency in biofilm dissolution, a quality of particular significance because it is a pivotal step in mitigating antimicrobial resistance and fostering expedited wound healing. The confluence of BBD's enzymatic abilities and biofilm-removing properties, as well as its delivery via a GV helps maintain proper moisture balance, thereby fostering an optimal microenvironment for wound healing.

The prospect of BBD in debridement, the formation of granulation tissue, and angiogenesis becomes even more promising when paired with the evidence of bromelain's diverse abilities. While some of bromelain's abilities relating to the debridement of chronic wounds have not been studied directly in clinical trials, as one reviews the literature on bromelain, its applicability and role in the mechanism of action of BBD becomes more apparent. Bromelain from the pineapple stem may exhibit potent antimicrobial efficacy by modulating the activation of NK cells, INF-γ, and TNF-α, which is crucial for fostering the immune response mediated by granulocytes and macrophages, and essential for combating infection. Additionally, bromelain exerts nuanced control over inflammatory cascades by regulating the secretion of inflammatory mediators such as IL-1, IL-6, and PGE-2 via inhibition of COX-2, thus ensuring a balanced inflammatory milieu conducive to healing. Finally, bromelain may aid in edge preparation by stimulating TGF-β production, which is pivotal for producing robust granulation tissue, epithelialization, and angiogenesis.

Altogether, the properties of bromelain and the hypothesized synergistic effects of BBD underscore its efficacy in establishing a conducive wound microenvironment that is primed for efficient tissue repair and regeneration.

## Limitations

This analysis has some limitations. First, some of the positive wound healing effects of bromelain that were described in publications regarding bromelain's systemic effects and preclinical studies have not yet been demonstrated in randomized clinical trials. These positive effects need to be translated to the wound care arena and demonstrated in clinical studies that specifically focus on BBD products to draw further, more concrete conclusions on BBD's mechanism of action. Second, although the authors of the present review performed due diligence in evaluating all articles cited herein, a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) analysis was not performed. Thus, this article is a literature review, as opposed to a systematic review or meta-analysis, and some of the articles cited may have methodological inconsistencies.

## Conclusion

The efficacy of BBD is largely due to the substrate's ability to effectively address many facets of the TIME model of wound healing and underscores its potency as a strategic pivotal component for managing chronic hard-to-heal wounds. BBD not only demonstrates remarkable wound healing capabilities but also introduces speed of action in its therapeutic action, thus positioning it as a secure and expedient therapeutic option. Additional research across diverse wound classifications holds promise for the emergence of BBD as a novel standard for use in managing chronic ulcerations.

## Author & Publication Information

**Authors:** Robert Snyder, DPM, MSc, MBA[1,2]; Timothy Hoffmeister, BS[1]; Joey Karim Ead, DPM, MS[3]; Anwar Nass, MBS, BS[1]; Ety Klinger, PhD, MBA[2]; Keren David-Zarbiv, MSc, BS[2]; Yael Kats-Levy, PhD[2]; and Aya Ben Yaakov, PhD, MSc, BS[2]

**Affiliations:** [1]Barry University School of Podiatric Medicine, Miami Shores, FL, USA; [2]MediWound, Ltd, Yavne, Israel; [3]Christus Health System, Alexandria, LA, USA

**Disclosures:** R.S. serves as Chief Medical Officer of MediWound, Ltd. E.K., K.D-Z., Y.K-L., and A.B.Y. are employees of MediWound, Ltd.

**Correspondence:** Robert Snyder, DPM; Barry University, 7301 N. University Drive, Tamarac, FL 33321; drwound@aol.com

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