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Review on Probiotics as Wound Healers: Mechanisms of Action and Clinical Outcomes

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Abstract

A wound is an injury to living tissue that can vary in severity from minor scratches and abrasions to deep lacerations, and punctures. They often require medical attention to prevent infection and promote healing. Conventional approaches to wound care frequently utilize antiseptics and antibiotics, which may occasionally impede the healing process and lead to antibiotic resistance. Recent research has explored alternative treatments, with probiotics emerging as a promising option due to their beneficial effects on wound healing. Recent research indicates that certain probiotic strains can enhance wound healing through multiple mechanisms. Studies have shown promising results in both *in vitro* and *in vivo* models, demonstrating accelerated wound closure rates and improved healing outcomes. Applying probiotics in wound care could offer a novel, cost-effective approach to treatment, potentially reducing the use of antibiotics and addressing challenges posed by antibiotic-resistant bacteria. This review examines the potential role of probiotics in wound healing, focusing on the mechanisms through which they exert their effects, their clinical applications, and the current evidence supporting their use. It examines how probiotics can influence the wound healing process through modulation of the immune system, production of antimicrobial substances, and enhancement of epithelial barrier function.

Keywords: Probiotics, skin wound, adhesion, encapsulation, wound healing

Introduction

Wounds are a significant global health issue, often leading to severe complications if not managed properly. Despite advancements in therapies and wound care management, the number of patients suffering from wounds continues to rise (1). Wounds can be broadly categorized into two main types: acute and chronic. Each type has distinct characteristics and implications for treatment and healing(2). Acute wounds are injuries that occur suddenly and typically heal in a predictable and timely manner. They often result from trauma, surgical procedures, or accidents (3). Acute wounds encompass a variety of injuries, including abrasions, punctures, burns, incisions, and lacerations, each requiring specific management strategies to promote healing and prevent complications (4). Chronic wounds are wounds that fail to progress through the normal stages of healing within the expected timeframe (usually around 4-6 weeks). These wounds often get stuck in the inflammatory phase and do not heal properly due to various underlying factors such as poor blood flow, infection, or systemic conditions (5). Chronic wounds include all types of ulcers namely diabetic ulcers, pressure ulcers, and arterial with delay in healing and lead to severe complications (6). This is particularly true for individuals with conditions like burns, diabetes mellitus, or those who are immuno-suppressed, as these groups are more prone to chronic or non-healing wounds.

A complete approach for effective wound treatment demands the connotation of a multidisciplinary team. This collective approach guarantees thorough care that not only targets the wound itself but also considers the underlying conditions and individual patient factors that influence the

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healing process. In this context, probiotics present a ground-breaking, bioactive method by utilizing the advantageous properties of specific bacterial strains to promote wound healing. Conventionally recognized for their role in gut health and digestive wellness, probiotics are increasingly being recognized within the realm of wound care. These beneficial microorganisms, which include certain bacteria and yeasts, are paving the way for new treatment potentials for various wound types (7). The basis behind retaining probiotics for wound healing is rooted in our advancing comprehension of the human microbiome and its vital contribution to overall health, including skin integrity. Similar to how probiotics can restore evenness to the gut microbiome, studies suggest they may also positively affect the skin's microbial environment, thereby facilitating quicker and more effective wound recovery (8).

This ground-breaking approach to wound management is particularly notable in rising issue of antibiotic resistance. Probiotics may serve as an alternative or complementary option that need on antibiotics while addressing the infectious components of wound healing (9). The application of probiotics in this context includes a broad spectrum of potential advantages, including the reduction of inflammation, and the stimulation of tissue repair mechanisms (10). As research in this field advances, probiotics are emerging as a promising asset in the wound toolkit, potentially transforming our methods of treating wounds, particularly those that are chronic or challenging to heal. This study will focus on the application of probiotics in conjunction with growth factors to expedite the wound-healing process, aiming to enhance the body's inherent healing abilities and provide hope for more quick recovery.

Wound Repair Mechanism

Wound repair is a complex process that restores the damaged tissue. It involves a series of cellular and molecular events to replace damaged tissue, and restore normal function. The wound healing process is basically divided into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Each phase is very important to ensure the proper wound healing and minimize complications such as infection or chronic wounds (Fig. 1).

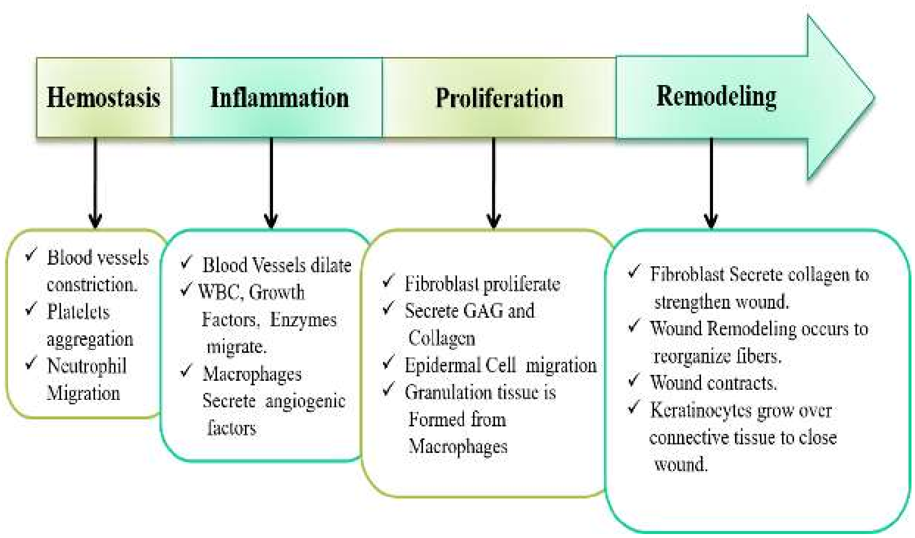

Fig 1: Stages of wound healing

Probiotics as Wound Healers

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a. *Hemostasis*

After injury, the body's first response is to prevent blood loss and seal the wound. Hemostasis is the body's mechanism for clotting, which serves as the blockade against further damage (11). Blood vessels around the wounds, would tighten the reduce blood flow, minimizing blood loss. Platelets adhere to the exposed collagen in the damaged tissue and aggregate, forming a plug. The chemicals like adenosine diphosphate (ADP) and thromboxane A2, were released to attract more platelets. The coagulation cascade was activated, wherein fibrinogen is converted to fibrin, which forms a stable clot (12). The clot stops blood loss and acts as a scaffold for incoming cells that will help repair the wound.

b. *Inflammation*

The next stage is Inflammation (Cleaning and Defense), which occurs within hours to a few days after the injury. This stage is serious for cleaning the wound of debris and bacteria while signaling for tissue repair. Neutrophils are the first immune cells to reach at the site, typically within minutes to hours. They are responsible for phagocytosing (engulfing) bacteria, dead cells, and debris. After 24–48 hours, macrophages substitute neutrophils and continue to clean the wound. Macrophages also liberate cytokines and growth factors, such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), which promote tissue repair and angiogenesis. Blood vessels expand to release of histamines and other signaling molecules. This increased blood flow, allows immune cells, nutrients, and oxygen to reach the wound (13). Inflammatory cytokines like interleukins (IL-1, IL-6), tumor necrosis factor-alpha (TNF-α), and chemokines are released, recruiting more immune cells and fibroblasts to the wound site.

c. *Proliferation Stage*

The third stage is proliferation (tissue formation). This phase naturally begins within a few days of the injury and can last weeks, depending on the wound's size and severity. This is the phase where new tissue and blood vessels are formed. Fibroblast migration occurs at this stage which migrate to the wound site and start producing collagen, forming the new tissue's structural framework. Initially, collagen type III is laid down in a random pattern to provide early strength to the wound. Macrophages secrete Vascular endothelial growth factor (VEGF), which helps in formation of new blood vessels from pre-existing ones. A pink, soft tissue called granulation tissue are formed which composed of fibroblasts, collagen, new blood vessels, and immune cells fills the wound bed and provides the basis for further healing (14). Keratinocytes (skin cells) migrate from the edges of the wound or hair follicles and cover the wound bed, forming a new epithelial layer. These cells undergo proliferation and differentiation to restore the skin barrier.

d. *Remodelling stage*

The last stage is remodeling (Maturation and Strengthening) which can last for months to years. This phase mainly focuses on improving the tensile strength and functionality of the newly formed tissue. Initially, the wound contains randomly arranged collagen type III and over time, collagen type III is replaced by collagen type I, which are stronger and more organized in arrangement with skin tension lines which increases the mechanical strength of the tissue (15). The formation of scar was initiated by shrinking and pulling the cells edges of the wound closer together by special cells called myofibroblasts. Although the wound is mostly healed, the scar tissue never recovers full strength (only about 70–80% of the original strength). Wound healing is a multifaceted process that requires the detailed management of cellular events and signaling molecules. Disruptions in any of these phases could result in delayed healing (16). By understanding the mechanisms of wound healing mechanism, novel therapies such as growth factors, stem cells, and

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probiotics are being explored to enhance healing and reduce complications.

Probiotics available at the market

Probiotics are live microorganisms that confer a health benefit on the host when given in adequate amounts. The first discovered probiotic was a certain strain of bacillus found in Bulgarian yogurt, called *Lactobacillus bulgaricus*. Stamen Grigorov, the Bulgarian physician, and microbiologist, discovered the discovery in 1905. Recent theories are normally credited to Russian Nobel laureate Élie Metchnikoff, who postulated around 1907 that yoghurt-consuming Bulgarian peasants lived longer (17). This made the probiotic market grow unbelievably. These useful bacteria and yeasts are naturally found in the human body, particularly in the gut, and are also present in various fermented foods and dietary supplements (18). Probiotics helps in preserving a healthy balance of gut microbiota, improving digestive health, boosting the immune system, and gastrointestinal disorders (19). The knowledge of probiotics and their roles can help in selecting the suitable strains for targeted health benefits (20). Several genera of probiotics are commonly used for their health benefits, each contributing uniquely to maintaining and restoring health (Fig. 2). Among these, *Lactobacillus, Bifidobacterium, Streptococcus, Saccharomyces*, *Enterococcus, Bacillus, Leuconostoc,* and *Propionibacterium* is most notable.

Lactobacillus

Lactobacillus is the largest group of lactic acid bacteria. Lactobacilli are phylogenetically grouped into seven groups based on their 16S rRNA sequences. Among them, *Lactobacillus acidophilus, Lactobacillus rhamnosus, and Lactobacillus plantarum* are the most widely known probiotic genera, found in fermented foods such as yogurt, kefir, and sauerkraut (21).

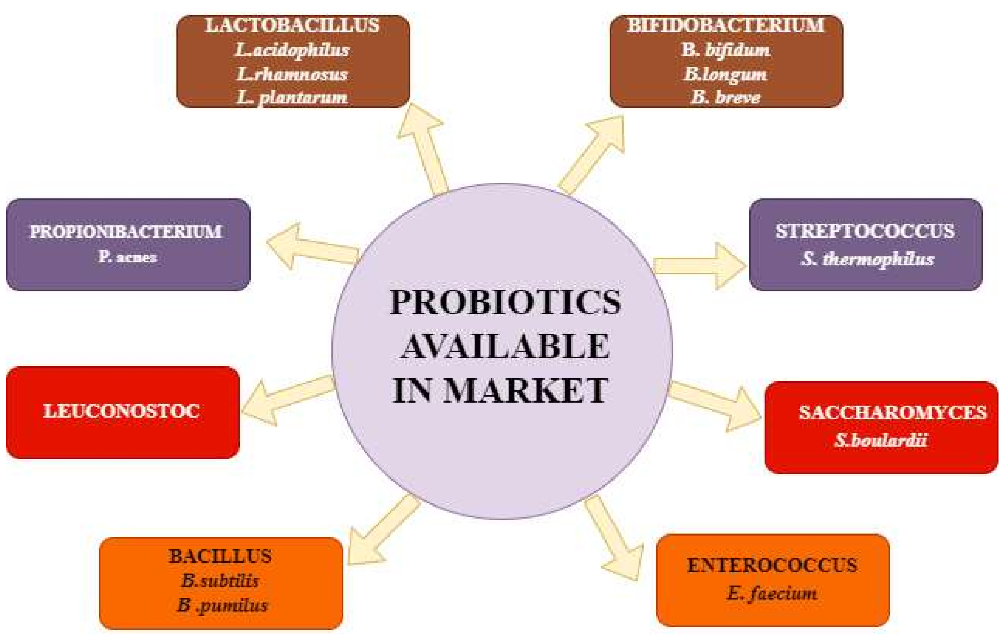

Fig 2: Schematic Representation of different types of Probiotics available in the market

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It is known for digestive health and immune function. *Lactobacillus acidophilus* improves digestion, helps with lactose intolerance, and also balance immune function. *Lactobacillus rhamnosus* is effective against gastrointestinal infections and supports the immune system. It is also effective in preventing and treating diarrhoea. *Lactobacillus plantarum* species helps to cure bowel syndrome, improve digestion, and supports the gut health (22). The functions of these probiotics include balancing the gut microbiota by inhibiting pathogenic bacteria, producing lactic acid, hydrogen peroxide, and bacteriocins to fight harmful microorganisms, enhancing the immune response, and enhancing the gut barrier.

Bifidobacterium

Bifidobacterium is mostly found in the intestines and is crucial for digestive health and maintaining a balanced gut microbiota. Species like *Bifidobacterium bifidum* aids in digesting dietary fiber and producing vitamins. *Bifidobacterium longum* eases gastrointestinal discomfort and improves lactose tolerance. *Bifidobacterium breve* improves gut health and immune function (23). Their functions include in creating short-chain fatty acids (SCFAs) like acetate and butyrate, which nourish the gut lining (24). It helps in the digestion of complex carbohydrates and fibres and also decreases inflammation and promotes a healthy immune response (25).

Streptococcus

Streptococcus is a bacterial genus which are non-motile, gram-positive cocci that measure between 0.5 and 2μm (26, 27). Streptococcus species are grouped based on their haemolytic properties. Streptococcus species are known pathogens but some strains are used as probiotics due to their beneficial effects**.** Among the beneficial ones, *Streptococcus thermophilus* is widely used as a probiotic in dairy fermentation. Its ability to improve lactose digestion and contribute to gut health highlights its importance in both nutrition and probiotic therapy (28).

Saccharomyces

Saccharomyces species are model organism and also known as a valuable tool for various applications. As a probiotic, the strain *Saccharomyces boulardii* is effective in treating and preventing gut issues (29, 30). It produces antimicrobial substances that inhibit the pathogenic bacteria at the wound sites. They are given as a topical medicine to hasten the wounds.

Enterococcus

Enterococcus is a genus of gram-positive, facultative anaerobic bacteria that are found in the gastrointestinal tracts of humans and animals. Some species of Enterococcus are known to cause infections, particularly in hospital settings, but certain strains of Enterococcus have shown their potential in wound healing due to their probiotic properties and ability to fight against pathogens (31). The lactic acid, produced by Enterococcus strains can lower the pH of the wound environment inhibit the growth of pathogenic bacteria, and enhance the activity of immune cells involved in wound healing. *Enterococcus faecium* strains can disrupt biofilms formed by pathogenic bacteria (32, 33). Biofilms usually protect the bacteria from the immune system and antibiotics, making infections difficult to treat. By breaking down biofilms, Enterococcus can help clear infections and improve wound healing outcomes.

Bacillus

Bacillus subtilis and *Bacillus pumilus*, are recognized as a novel wound healers due to their antimicrobial properties, and their ability to endorse wound-healing processes. Bacillus species produce antimicrobial peptides (AMPs) which can inhibit the growth of pathogenic bacteria found in wound area. They also produce enzymes like proteases and lipases which can degrade biofilms and thereby avoiding infection (34). Secretion of lipopeptides helps in cleaning the wound sites and promotes tissue regeneration. Bacillus species are natural and effective approach to

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wound healing, leveraging their antimicrobial, immunomodulatory, and regenerative properties.

Leuconostoc

Leuconostoc sp., has garnered interest in the field of wound healing due to its unique properties. Leuconostoc produces antimicrobial compounds such as bacteriocins and organic acids (e.g., lactic acid) which helps in inhibition of pathogenic bacteria which commonly infect wounds, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa.* Leuconostoc disrupts biofilms which enhance the effectiveness of other antimicrobial treatments (35). Leuconostoc controls the immune response, reducing inflammation and also balance the skin microbiome, promoting beneficial bacteria while suppressing harmful ones. Leuconostoc can be incorporated into creams, gels, and ointments applied directly to wounds. These topical treatments influence their antimicrobial and biofilm-disrupting properties (36).

Propionibacterium

Propionibacterium acnes (recently reclassified as *Cutibacterium acnes*), is a bacterium that is primarily known for acne. However, certain species have potential applications in wound healing by producing antimicrobial peptides and bacteriocins which can inhibit the growth of pathogenic bacteria (37). Propionibacterium plays a dual role in modulating the immune response and also reduce inflammation which are more beneficial in the wound-healing process, and can also delay healing and lead to severe complications (38). Advanced wound dressings filled with Propionibacterium to provide continuous antimicrobial protection and supports a balanced wound microbiome (39).

Mechanism of Action

Probiotics as supplements showed many health benefits, particularly for digestive health, immune function, and potentially mental well-being (40). Probiotic supplements are increased in the market to meet the healthy balance of an individual. It exhibits various mechanisms to promote health care. Apart from these supplements, probiotics as topical applications showed a positive potential in healing wounds. Studies reveal that any topical application of probiotics in the form of any wound dressing material effectively heals the wound (41). The various mechanisms involved in the curing of wounds may include, modulation of the immune system, antimicrobial properties, enhancement of epithelial cells, and modulation of the microbiome (42).

Probiotic Modulation of Immune Responses

Probiotics controls the immune response by promoting a balanced inflammatory reaction that important for effective wound healing. They enhance the activity of macrophages and neutrophils, improve the production of anti-inflammatory cytokines, and suppress pro-inflammatory cytokines (43). Probiotics stimulate macrophages to improve phagocytosis and the production of reactive oxygen species (ROS) and nitric oxide (NO), at the wound sites. Probiotics interacts with dendritic cells for their maturation and enhancing their antigen-presenting capabilities (44). These probiotics also stimulate the Toll-like Receptors which helps the production of anti-inflammatory cytokines like IL-10 and TGF-β (45). The immune-modulating effects of probiotics are multifaceted and involve complex interactions with both immune cells and the gut microbiota (46). Probiotics play vital role in maintaining immune homeostasis and protecting against various diseases by increasing innate and adaptive immunity, restoring microbial balance, and strengthening mucosal barriers. Research studies had shown that specific strains of probiotics have an impact on anti-inflammatory effects by reducing excessive inflammation, which is vital for optimal wound healing. The strains like *Lactobacillus* and *Bifidobacterium*, controls the production of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. By reducing these pro-inflammatory mediators, probiotics helps in

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severity and duration of the inflammatory response, preventing tissue damage caused by prolonged inflammation (47,48).

Antimicrobial Properties of Probiotics

Probiotics produce a wide range of antimicrobial substances, such as bacteriocins, organic acids, and hydrogen peroxide, at the site of the wound to respond the growth of harmful organisms (49, 50). Bacteriocins, are protein-based toxins produced by probiotics, effectively delay the spread of pathogenic bacteria. The production of lactic acid and acetic acid by probiotics helps to lower the pH of the wound environment and creates negative conditions for the survival of pathogenic and biofilm microbes (51, 52). Certain probiotics also produce hydrogen peroxide, which exhibits antimicrobial properties against a wide range of microorganisms.

Probiotic-Mediated Epithelial Cell Fortification

The use of probiotics to improve epithelial cells at wound sites, improves the production of extracellular matrix components like collagen, which play a crucial role in providing structural support for the creation of new tissue (53). Probiotics are getting noticed for how they attract epithelial cells to wound sites. This has an impact on boosting ECM component production, like collagen. It's crucial to provide the structural support needed to create new tissue. This process also helps support the epithelial barrier. It does this by promoting tight junction protein expression and assembly (54). These proteins are key to stop pathogens from invading and to minimize fluid loss from the wound. Probiotics also help create a healthy microbial community making a good environment to heal. Some probiotics can even break down biofilms that antibiotic-resistant bacteria form, which can slow healing. Studies show that strains like *Lactobacillus* and *Bifidobacterium* can boost epithelial cell growth, migration, and barrier function. Animal studies back this up and reveal that probiotics can speed up wound healing and improve regenerated tissue quality. For instance, putting *Lactobacillus rhamnosus* right on mouse wounds has been shown to speed up healing and reduce inflammation. Wound healing involves making Reactive Oxygen Species (ROS). These are essential to kill microbes and for signaling, but too much can harm. Probiotics have antioxidant properties that help manage oxidative stress at the wound site (55).

Certain probiotic strains, like Lactobacillus plantarum and Bifidobacterium longum, make antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase. These enzymes fight ROS and shield wound tissue from oxidative harm. This matters a lot in chronic wounds where too much ROS can slow healing by hurting proteins, lipids, and DNA in the wound area. Probiotics produce exopolysaccharides (EPS) and other bioactive compounds that attract the free radicals and lower oxidative stress (56, 57). By removing oxidative damage, probiotics set up a better environment for cells to move, grow, and regenerate the new tissue. Probiotics can boost collagen production by exciting fibroblasts. Collagen is key for keeping healing tissue strong, and proper collagen reshaping in the later parts of wound healing ensures strong working tissue forms with less scarring. Many clinical trials have also shown good results in humans (58). One study on diabetic foot ulcers found that putting probiotics on the skin led to faster wound healing than usual treatments. Together, these findings highlight how probiotics improve epithelial cell function and help wounds healing.

Evidence for Clinical Studies

Probiotics known for helping digestion, might also help heal wounds (59). People can use probiotics on wounds by putting them right on the skin taking them by mouth, or using bandages with probiotics in them (60). Putting probiotics on the skin aims to keep skin healthy, treat skin problems, and help wounds heal. Figure 3 shows how

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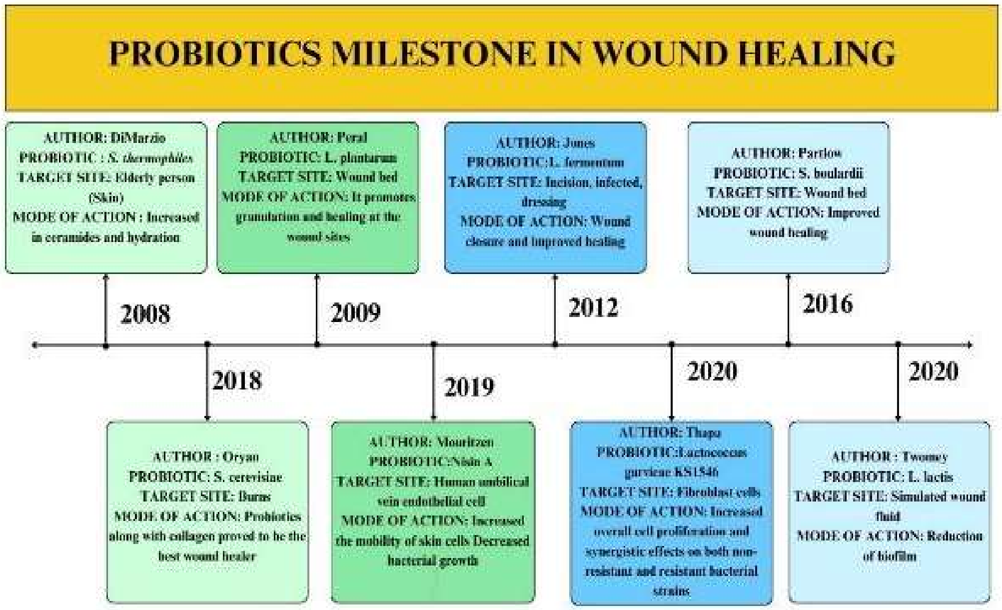

Fig 3: Breakthroughs in wound healing process using probiotics

probiotics make a big change in wound healing. This idea comes from thinking that, like the gut, the skin has its own group of tiny living things that help keep the skin strong, fight off germs, and stay healthy overall (61). People have made creams, gels, and bandages with probiotics to put good bacteria right where the wound is (62). These seem to make wounds heal faster and get infected less often. Foot ulcers are a common complication of diabetes which are difficult to treat. A clinical trial in 2016 discovered the positive effects of *Lactobacillus plantarum* on chronic diabetic foot ulcers. Patients who received topical applications of probiotics showed significant improvement in wound healing compared to the control group. The probiotic-treated wounds had faster healing rates and better infection control, maybe due to the probiotic's ability to control the local microbiome and reduce swelling (54). Another study investigated the use of probiotic-based dressings on burn wounds, focusing on *Lactobacillus rhamnosus* in the animal model study reduced the bacterial colonization, promoted tissue regeneration, and enhance wound healing. Researchers had confirmed that the probiotic created an environment that encouraged beneficial bacterial growth while inhibiting harmful pathogens in their studies (55).

The clinical studies on oral probiotics, reveals that it has hastens the wound healing by using the strains of *Bifidobacterium* and *Lactobacillus*. Patients who received probiotics had experienced fewer wound infections and faster healing compared to that of control group. The studies also suggested that oral probiotics controls systemic inflammation and immune responses, indirectly enhancing wound healing (65).

In a clinical trial, *Bacillus coagulans* were tested for its effect on pressure ulcers in elderly patients. It was found that there was a significant reduction in wound size and faster healing rates in patients who received the probiotics compared to those on standard care. Studies revealed that the probiotics also had reduced infection rates, suggesting that probiotics might enhance innate immune

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responses (66). The evidence so far suggested that specific strains like Lactobacillus plantarum and *Bacillus coagulans* plays a beneficial role in managing wounds, especially in diabetic and elderly patients (67).

Oral probiotics, when managed in suitable amounts, confer a health benefit to the host by refining or restoring the natural balance of the oral microbiome. They are increasingly being researched and used for their potential benefits in oral health (56). Several strains of probiotics reduce the growth of *Streptococcus mutans*, a key bacterium involved in the formation of cavities. Probiotics assist in the management of oral thrush by outcompeting with Candida species for attachment sites and nutrients. By competing with pathogenic bacteria, regulating the immune response, and generating substances that hinder harmful bacteria, probiotics can aid in reducing inflammation and enhance the periodontal health. Probiotics can decrease the levels of foul-smelling volatile sulphur compounds by suppressing the bacteria responsible for their production (57). Commonly utilized strains include *Lactobacillus reuteri, Lactobacillus rhamnosus, Bifidobacterium lactis,* and *Streptococcus salivarius* (58).

Wound dressings with probiotics is an innovative method for wound care in healing and preventing infections (62). These dressings utilize the useful properties of probiotics to boost a healthy balance of microorganisms in the wound area, potentially resulting in improved outcomes for wound treatment. Probiotics can delay the growth of harmful bacteria by competing for resources, producing antimicrobial substances, and influencing the immune response (68, 70). The wound healing was eased by probiotics through the development of local immune responses, reduction of inflammation, and promotion of the growth of healthy tissue. Probiotics have the potential to regulate the body's inflammatory response, helping to reduce chronic inflammation which hinders the wound healing. Probiotics also helps in disrupting biofilms, which are complex communities of bacteria that are highly resistant to antibiotics which complicate wound healing (69).

The clinical trials were conducted over several decades have explored the use of probiotics as a new type of wound healer (Table 1). Probiotics work by competing with harmful bacteria for adhesion and nutrients at the wound sites, thus promoting healing. The Probiotics produce lactic acids, hydrogen peroxide, and bacteriocins, which helps in antimicrobial activity for wound healing (71, 72). These probiotics wound dressing materials helps in advancing wound care, preventing infections, reducing inflammation, and also promotes quick and more efficient wound healing. As research advances, these innovative wound dressings become a standard part of advanced wound management techniques.

In vitro and *In vivo* studies on probiotics in wound healing

a. *In vitro* studies

Probiotics have been studied both *in vitro* and *in vivo* for their possible to support in wound healing, mainly by their ability to control immune responses, inhibit pathogenic bacteria, and promote tissue repair (89, 90). Several in vitro studies have demonstrated that probiotics especially *Lactobacillus sp*. which can inhibit the growth of common wound pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. It is due to the production of bacteriocins, organic acids (e.g., lactic acid), and other antimicrobial compounds which lowers the pH and inhibit pathogen colonization. The studies also found that the supernatant of the probiotics had a powerful antimicrobial effect. *In vitro* models using keratinocytes or fibroblasts has revealed that these probiotics can control the release of pro-inflammatory cytokines (such as TNF-α, and IL-1β) and anti-inflammatory cytokines (like IL-10), which are crucial for balanced wound healing. Research on *Lactobacillus rhamnosus* GG (LGG) demonstrated that the probiotic could reduce

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Table 1: Clinical trials conducted over several decades using probiotics as wound healer

Target Sites	Probiotics Used	Mode of Action	Ref
Oral mucosa	L. reuteri	Impact on matrix metalloproteinase and interferon	(59)
Simulated wound fluid	Nisin A Bioengineered L. lactis	Reduction of S. epidermidis biofilm	(60)
Erythrocyte solution Murine 3T3 cell cultures	Nisin bonded with gellan gum (a biocompatible polysaccharide)	The gellan-nisin conjugate kept its antimicrobial properties even with heat alkali treatment at 80 ◦C or chymotrypsin digestion Showed good biocompatibility Prevented S. epidermidis cells from adhering to normal animal cells	(61)
Venous ulcer	L. plantarum	Reduction of bacterial load, increased immune cells, modified inflammatory production, and increased healing	(62)
Wound bed	L. plantarum	promotes granulation and healing and significantly improves healing	(63)
Burns (animal study)	L. plantarum	Improved tissue repair, phagocytosis, and apoptosis at the wound sites	(64)
Elderly person (skin)	S. thermophiles	Increased in ceramides and hydration	(65)
In vitro studies	Nisin (a polycyclic polypeptide produced by Lactobacillus lactis	Release of antimicrobial activity against S. aureus.	(66)
In vitro studies	Lysozyme and Nisin (a polycyclic polypeptide produced by Lactobacillus lactis	1. Inhibited the growth of B. subtilis and S. aureus 2. Inhibited the formation of S. aureus biofilm	(67)
Burns (animal study)	S. cerevisiae	Probiotics along with collagen proved to be the best wound healer	(68
Keratinocyte cells	Lactobacillus plantarum	Promoted wound re-epithelization and neo-vascularization	(69)
In vitro studies	Nisin (a polycyclic polypeptide produced by Lactobacillus lactis	Inhibited the growth of gram-positive and gram-negative bacteria	(70)
Incision, infected, dressing	L. fermentum	Wound closure and improved healing	(71)
Human umbilical vein endothelial cell	Nisin A	Increased the mobility of skin cells Decreased bacterial growth	(72)
Fibroblast cells	Multi-peptide bacteriocins from Lactococcus garvieae KS1546	Increased overall cell proliferation A combination of two or more antimicrobial agents can have synergistic effects on both non-resistant and resistant bacterial strains	(73)
Wound bed	S. boulardii	Improved wound healing	(74)

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inflammatory responses in human keratinocyte cultures, suggesting a protective role in skin health and wound healing (75–77). Probiotics have been shown to enhance the proliferation and migration of fibroblasts, keratinocytes, and endothelial cells in wound models. These processes are essential for the formation of new tissue and blood vessels in healing wounds. Research studies found that *Lactobacillus plantarum* promoted the migration of keratinocytes and fibroblasts, which are necessary for wound closure (78, 79).

b. *In vivo* studies

In vivo studies provide a complete view of how these probiotics function within a living system. Several studies using animal models (such as rats and mice) have demonstrated the beneficial effects of probiotics on wound healing. The application of probiotics to wounds resulted in faster re-epithelialization, reduced inflammation, and improved collagen formation, which are crucial steps in wound healing. Several research studies revealed that *Lactobacillus plantarum* applied on diabetic mice led to faster wound closure, increased collagen synthesis, and improved vascularization, which were vital for wound repair mechanism in diabetic conditions. The evidence suggests that probiotics can improve wound healing, particularly for chronic wounds and post-surgical recovery.

It has been absorbed that probiotics when taken orally influence wound healing through the gut-skin axis, where gut microbiota regulate immune responses which affect skin health. Some *in vivo* studies suggest that oral probiotics can promote systemic anti-inflammatory effects, which may benefit wound healing indirectly. The oral application of *Lactobacillus rhamnosus* on mice showed a faster wound healing by reducing inflammation and promoting a balanced immune response at the sites. In the recent research studies, *Lactobacillus rhamnosus GG* found to regulate cytokine production in keratinocytes and fibroblasts, resulting in an increased inflammatory response crucial for the initial stage of wound healing. Probiotics also boost the production of key cytokines like IL-6 and TNF-α, which plays a significant role in coordinating the immune response during wound healing.

Recent findings indicate that *Bifidobacterium breve* improves tight junction protein expression in epithelial cells, reinforcing the epithelial barrier and improving skin barrier function. This enhanced barrier function aids in warding off pathogen infiltration and maintaining a moist wound environment, for optimal healing. Recent studies revealed that diabetic mice treated with a topical application of *Lactobacillus reuteri* showed a accelerated wound closure and enhanced collagen synthesis compared to the control group. The oral intake of *Lactobacillus fermentum* in a rat model of burn wounds also resulted in decreased inflammatory markers and hasten the wound healing. Application of probiotics controls the inflammation by lowering the level of inflammation that can hinder wound healing (80, 81). The application of *Lactobacillus acidophilus* to chronic wounds in a rabbit model significantly reduced the formation of *Pseudomonas aeruginosa* biofilms (82, 83). Probiotics can disrupt biofilms, which are resistant to antibiotics and impede wound healing, which can enhance the effectiveness of standard treatments (84). Both *in vitro* and *in vivo* studies provide promising evidence that probiotics can be effective in improving wound healing, particularly by modulating inflammation, promoting tissue regeneration, and preventing infections.

Challenges and future directions

Obstacles to Probiotic Wound Healing Applications

Application of probiotics has appeared as a hopeful strategy for enhancing wound healing by modulation of the skin microbiome, facilitation of tissue repair, and the fight against pathogenic infections. However, several challenges and potential avenues for future research must be addressed for probiotics to gain acceptance

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as a standard therapeutic option in wound care. The investigation of synergistic effects of various probiotic strains and developing personalized multi-strain combinations proved that they can enhance the healing process. In recent years, innovations such as microencapsulation and advanced packaging techniques have been utilized to enhance the stability and viability of probiotics within wound dressings. The combination of important materials on wound area alters the pH and infection markers to release probiotics in a controlled manner represents a good approach to wound management. Advanced diagnostic tools to assess the microbiome of individual wounds and customize probiotic treatments are essential. Not all probiotic strains have the same effects, the benefits of one strain do not necessarily translate to another. This strain specificity makes it difficult to standardize probiotic therapies for wounds. Finding the right strains that are effective in diverse wound types is challenging, and the mechanisms behind strain efficacy remain insufficiently understood. Probiotics when utilized as medical treatments, are classified under both medical and dietary supplement categories, which complicates the establishment of standardized protocols for their production, storage, and application (85). The application of conventional methods, such as creams or dressings, are not effective, because of various environmental factors, including pH levels, oxygen availability, and the presence of exudates, which can influence bacterial survival on the wounds. Although probiotics are generally considered as safe, the introduction of live bacteria into an open wound may lead to a risk of infection. The probiotics interact with pre-existing microbial communities, potentially resulting in unexpected complications.

Future Directions

Future research should focus on identifying the probiotic strains most effective for different types of wounds, such as diabetic ulcers, surgical wounds, or pressure sores. Understanding the mechanisms of action, such as their role in modulating immune responses, producing antimicrobial peptides, or influencing collagen synthesis, could lead to more effective strain selection (86). As our understanding of the skin microbiome advances, there is potential to develop personalized probiotic treatments tailored to an individual's specific microbiome composition and wound characteristics. This personalized approach could improve efficacy and reduce the risk of adverse effects (87). Innovations in delivery systems will be crucial for enhancing the viability and efficacy of probiotics in wound healing. For example, encapsulation techniques, bioengineered dressings, or slow-release systems could be explored to protect probiotics in hostile wound environments and ensure their prolonged action. Combining probiotics with prebiotics (substrates that promote the growth of beneficial bacteria) or postbiotics (metabolic products of probiotics) might enhance their therapeutic efficacy. This synergistic approach could promote faster wound healing and a more stable wound microbiome (88). In the future, we're likely to see a shift towards the more targeted probiotic treatments for wound healing. Different wounds—like diabetic ulcers, surgical wounds, or pressure sores could benefit from different probiotic strains, and figuring out which ones work best is a key area of research. Scientists are also trying to understand exactly how probiotics help: Do they calm inflammation? Kill harmful bacteria? Help the skin rebuild itself? The more we know, the better we can use them.

There's also a lot of buzz around personalizing these treatments. As the skin microbiome is unique, researchers focused on matching a probiotic treatment to specific skin type and wound condition which make healing faster and reduce the chances of any side effects. New technologies like protective capsules, smart wound dressings, or time-release systems are being investigated to keep probiotics alive and active where they're needed most. It has been found that there is a need for more large-scale, well-designed clinical trials to evaluate the efficacy, safety, and mechanisms of action of probiotics in

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wound healing. This paved the way for more standardized treatment protocols and regulatory approval for probiotic-based therapies. The Advances techniques in biology allows the development of bioengineered probiotics specifically designed for wound healing strategies. These strains were programmed to produce growth factors, antimicrobial peptides, or anti-inflammatory agents directly at the wound site. Probiotics could be used as part of a broader strategy to manipulate the wound microbiome, either by displacing harmful pathogens or promoting a more favourable environment for healing. The probiotics interaction with the native wound microbiome led to more targeted approaches like standardization and collaborating with regulatory bodies to establish a clear guideline for developing, testing, and approving probiotic wound dressings (89, 90). The advantages and proper application of probiotic-infused dressings through training programs and clinical guidelines are essential for maximizing the benefits of probiotic dressings in the future. Increasing patient awareness about the potential advantages of probiotics in wound care is key for nurturing the acceptance and adherence. The collaboration among microbiologists, material scientists, clinicians, and industry professionals help in driving innovation in probiotic wound care products. Future research should focus on strain specificity, improved delivery systems, and personalized therapies to maximize their potential.

Conclusion

Probiotics signifies a novel and promising strategy for wound care products. Their function by competing with harmful bacteria, generating antimicrobial compounds, and modulating the local immune response, aids in the management of wound infections. Their capacity to form biofilms and produce advantageous metabolites contributes to enhanced wound healing and tissue regeneration. The incorporation of probiotics into wound dressings presents considerable potential to improve healing outcomes and lessen dependence on conventional antibiotics, which is particularly relevant in light of the increasing issue of antibiotic resistance. This integration signifies an exciting advancement in both dermatology and microbiology; however, the field is still in its nascent stages and necessitates further comprehensive research before widespread clinical implementation. As components of the skin microbiome, these probiotics could positively affect the microbial equilibrium in the skin, particularly in wounds where the balance is interrupted. Wounds are often colonized by pathogenic bacteria, results in infections and delayed healing. Probiotics, including species such as *Lactobacillus* and *Bifidobacterium,* can suppress the proliferation of harmful bacteria by competing for essential nutrients, producing antimicrobial agents, and establishing an environment that is less conducive to pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. As an antimicrobial agent, these probiotics, generates bacteriocins and organic acids, such as lactic acid, which directly inhibit harmful bacteria at the wound site. This antimicrobial effect reduces the risk of infection, a important obstacle to wound healing, particularly in chronic wounds like diabetic ulcers.

Probiotics also play a significant role in modulating the immune response, which can facilitate wound healing. They activate local immune cells, such as macrophages and neutrophils, to eliminate dead tissue and pathogens, thereby supporting the initial phases of wound healing were controlling infection and clearing debris is essential. Moreover, probiotics influence inflammatory pathways. While inflammation is a natural response to wounds, excessive inflammation can result in tissue damage and hinder healing. Probiotics help to regulate this response by decreasing pro-inflammatory cytokines like TNF-α and IL-1β, while simultaneously promoting anti-inflammatory cytokines such as IL-10, thus fostering an environment conducive to tissue repair.

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Furthermore, probiotic treatment has been associated with accelerated re-epithelialization, largely due to its ability to enhance the proliferation and migration of keratinocytes, which are crucial for skin regeneration.

Probiotics also demonstrate potential in preventing biofilm formation by pathogenic bacteria, particularly Staphylococcus species, known for their biofilm production. By disrupting these biofilms, probiotics improve immune access and increase the efficacy of standard antimicrobial therapies. Current research on the efficacy of probiotics in wound healing primarily stems from animal studies. For example, experiments with diabetic mice suffering from chronic wounds have shown that the topical application of probiotics such as *Lactobacillus plantarum* can lead to significantly quicker wound closure, decreased inflammation, and enhanced collagen synthesis. Similar advantages have been observed in other animal models, including reduced bacterial colonization and improved tissue regeneration. While human clinical trial data is still limited, it is gradually increasing. Some smaller studies indicate that probiotics may be beneficial, especially in the prevention and management of infected wounds. One particular study involving burn patients found that a cream containing probiotics resulted in faster healing and lower infection rates compared to conventional treatments. A pilot study utilizing *Lactobacillus acidophilus* applied to surgical wounds reported quicker healing and fewer complications than a control group. However, the majority of human trials have been small-scale, and the findings are not yet definitive. Diabetic foot ulcers (DFUs) present a considerable clinical challenge due to issues like poor circulation and elevated infection risks. Some research has explored the role of probiotics in treating these persistent wounds, yielding encouraging results. For instance, a study combining *Bacillus coagulans* probiotics with standard treatments demonstrated improved healing rates and reduced infections in DFUs. Nonetheless, many of these studies suffer from limitations such as small sample sizes and insufficient power.

A key challenge in probiotic therapy is the variability among strains; different strains within the same species can produce markedly different outcomes in wound healing, and there is currently no agreement on which strains are the most effective. Furthermore, the selection of probiotics must be tailored to the specific type of wound, as certain strains may be more effective for chronic wounds than for acute injuries. The optimal method of delivering probiotics to wounds is still under investigation. While some studies favour topical application (e.g., creams, gels, or impregnated dressings), others suggest oral probiotics might have systemic benefits. Topical probiotics are more direct but face challenges in ensuring that they reach the wound bed in sufficient quantities. Some researchers are exploring the use of live probiotic dressings that slowly release bacteria over time to enhance their therapeutic effect. While probiotics are generally considered safe, their use in open wounds, particularly in immunocompromised individuals or those with severe burns, poses a potential risk of infection or adverse reactions.

As probiotics are live microorganisms, the risk of introducing new infections, especially in people with weakened immune systems, must be carefully considered. Additionally, regulatory hurdles for live microbial therapies are more stringent than for other wound healing treatments. The use of probiotics as a wound-healing treatment offers considerable promise due to their ability to modulate the immune response, reduce infections, promote beneficial microbiota, and enhance tissue repair. Early evidence, especially from animal studies and small human trials, supports their potential, but more high-quality, large-scale research is needed to establish clinical guidelines and optimize treatment protocols. Until then, probiotics remain a complementary rather than a primary treatment for wound healing, but they may evolve into a critical tool in modern wound care if ongoing research confirms their benefits.

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Declaration of Competing Interest

The authors have no conflict of interest.

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