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The role of topical probiotics on wound healing: A review of animal and human studies

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Abstract
Pathogenic, opportunistic, and commensal bacterial coexist in the intestinal tract, and imbalances among these strains have been linked to systemic inflammation and a variety of disease states. Similarly, human skin plays an important role as an interface between the body and the environment with an estimated 1 billion microbes per square centimetres. Skin microbiome fluctuations that cause increases in pathologic bacteria, either because of individual and/or environmental factors, can lead to disease states at the skin level ranging from inflammatory conditions to infections. As wounds are inherently associated with perturbations in the local microflora due to injury and activation of the immune responses, the addition of topical probiotics could be a means to prevent infection, regulate inflammation, and potentially augment healing. The goal of this review is to analyse the impact the skin microbiome has on cutaneous wound healing with a focus on developing proposed treatment algorithms and support for their therapeutic potential.

KEYWORDS
acute wound, biofilm, chronic wound, probiotics

1 | INTRODUCTION

The human gastrointestinal tract is home to an estimated 300 to 500 bacterial species, and the total number of bacteria in the gut is projected to be 10 times greater than the number of cells in the body.[1] Pathogenic, opportunistic, and commensal bacteria coexist in the intestinal tract, and imbalances among these strains have been linked to systemic inflammation and a variety of disease states.[2] Virulent bacterial species include *Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*,[3-5] while commensal strains include *Lactobacillus* and *Bifidobacterium*. Each individual hosts a unique biome that fluctuates daily based on diet, exercise, medications, surgical procedures, and stress.[3-11] Therefore, the gastrointestinal tract can be thought of as a constantly evolving and changing interaction between the external environment and one's internal milieu.

Similarly, human skin plays an important role as an interface between the body and the environment with an estimated 1 billion microbes per square centimetre.[12] The skin microbiome functions to promote local homeostasis by influencing the immune response.[13-17] Analogous skin microbiome fluctuations that cause increases in pathologic bacteria, either because of individual and/or environmental factors, can lead to disease states at the skin level, ranging from inflammatory conditions to infections.[3-11,18-20]

Therefore, any interventions that promote healthy bacteria and decrease pathologic bacteria should aid in wound healing. To that end, probiotics have shown efficacy in promoting cutaneous wound healing, regulating glucose homeostasis, decreasing inflammation, and improving various skin conditions.[21-31] A meta-analysis published in 2017 analysed six articles that explored topical and oral probiotics in animal models with cutaneous wounds. While they concluded that probiotics could be a useful treatment for cutaneous wounds, there was significant variability among the studies.[32] As wounds are inherently associated with perturbations in the local microflora because of injury and activation of the immune responses, the addition of topical probiotics could be a means to prevent infection, regulate inflammation, and potentially augment healing. The goal of this review is to analyse the impact the skin microbiome has on cutaneous wound healing with a focus on developing proposed treatment algorithms and support for their therapeutic potential.

Key messages

- as wounds are inherently associated with perturbations in the local microflora because of injury and activation of the immune responses, the addition of topical probiotics could be a means to prevent infection, regulate inflammation, and potentially augment healing
- topical probiotics have demonstrated efficacy in multiple human and animal models at augmenting numerous aspects of wound healing, but there are many unanswered questions; there is marked heterogeneity regarding the insult investigated, type and dosing regimen of the probiotic utilised, and a lack of standardised outcome measures
- the goal of this review is to analyse the impact the skin microbiome has on cutaneous wound healing with a focus on developing proposed treatment algorithms and support for their therapeutic potential

2 | WOUND HEALING AND TOPICAL PROBIOTIC: GENERAL STUDIES

Probiotics have demonstrated the ability in multiple human and animal models to improve wound-healing efficacy.[33-42] Probiotics of investigation have included *L. plantarum*, *kefir*, *L. fermentum*, and *S. cerevisiae* in thermal injury models, infected and non-infected wounds, and diabetic ulcers. In these studies, the mechanism of action was typically not explored, but topical probiotic treatment resulted in improved healing as demonstrated by increased granulation tissue deposition, improved collagen concentration, and stimulation of angiogenesis.[33-42] However, not all models demonstrated an improvement in topical wound healing with probiotics[33-44] (Tables 1 and 2).

3 | WOUND HEALING AND TOPICAL PROBIOTIC: PREVENTION OF INFECTION

To permit successful wound healing, bacterial counts must be below 10^5 organisms per gram of tissue and void of any beta-haemolytic *Streptococcus* bacteria.[45] As bacteria and exotoxins lead to local inflammation, they can interfere with epithelialization, contraction and collagen deposition and can suppresses macrophage-regulated fibroblast proliferation.[46] Thus, the prevention and treatment of wound infections is a crucial aspect of wound healing.

There are numerous options to prevent wound infections, such as silver dressings, iodine, and antibacterial skin products. While silver products have been used for over 2000 years because of their putative antimicrobial activity, a recent review found no convincing evidence that they have any effect on wound healing.[47-50] Iodine has been linked with cellular toxicity,[51] and topical antibiotics can lead to antibiotic resistance and contact dermatitis.[52,53] In contrast, topical probiotics are rarely associated with any systemic side effects and still retain their broad-spectrum antimicrobial activity. Kefir, a cultured probiotic beverage, has also shown to have topical antimicrobial activity against *Salmonella*, *Helicobacter*, *Shigella* and *Staphylococcus*, and *E. coli*.[54]

The mechanism of action by which probiotics are able to induce this antimicrobial effect has not yet been fully elucidated but is likely multifactorial. They produce exopolysaccharides that have immunostimulatory activity and are able to activate macrophages and lymphocytes.[55,56] In addition, probiotics have been shown to decrease the concentration of pathogenic bacteria via species-specific antagonism.[18-20,57,58] Another antimicrobial mechanism of action of probiotics is through the regulation of antimicrobial peptides (AMPs). AMPs are produced by a variety of cells (eg, mast cells, epithelial cells, and adipocytes) and help to maintain the integrity of the skin. They act to modulate the skin microflora via different mechanisms, leading to improved skin integrity, decreased inflammation, and are preventive against biofilm development. They have also been shown to augment cell proliferation and angiogenesis and, in combination with the aforementioned effects, create a

TABLE 1 Probiotics in wound healing: Animal studies

Author	Year	Treatment arms	Probiotic used	Dose	Finding
Valdez	2005	1. Burn 2. Burn/saline 3. Burn/PB	*L. plantarum*	200–300 CFU once	PB decreased BT improved tissue repair, phagocytosis, apoptosis
Rodrigues	2005	1. Punch with saline 2. Punch with neomycin-clobetasol 3. Punch with kefir	Kefir with *Leuconostoc* spp., *Lactobacillus lactis*, *Acetobacter* spp., *Saccharomyces cerevisae*, *Kluyveromyces marxianus*, and *K. lactis*	Unknown	Kefir enhanced wound healing measured by size and histology with improved granulation and neovascularisation
Jones	2012	1. Incision 2. Incision with dressing 3. Incision, infection 4. Incision, infected, dressing	*L. fermentum* between tegaderms	Unknown	PB increased wound closure and histologically showed improved healing
Huseini	2012	1. Burn 2. Burn/base gel 3. Burn/SD 4. Burn/kefir 24 hours extract 5. Burn/kefir 48 hours extract 6. Burn/kefir 96 hours extract	Extract from kefir grains at different time points	Unknown	Kefir gel improved healing directly related to extract length and all better than SD
Partlow	2016	1. Wound 2. Wound/PB	*S. bouladrii*	5 billion once	No improvement with healing or microbiome
Argenta	2016	1. Burns 2. Burns/PB 3. Burns/PA 4. Burns/PA/PB	*L. plantarum*	1×10^9 CFU daily to wound	Burns/PA/PB had decreased mortality versus Burn/PA. PB decreased septicaemia and production of inflammatory markers
Satish	2017	1. Burn 2. Burn/PB 3. Burn/PA 4. Burn/PB then PA	*L. plantarum*	3×10^8 CFU daily	PB decreased severity and length of infection, improved collagen concentration
Oryan	2018	1. Burn 2. Burn/SD 3. Burn/PB/SD	Unclear	Unclear	Kefir decreased inflammatory markers, stimulated wound healing, angiogenesis, wound contraction migration of fibroblasts, fibrous connective tissue formation
Oryan	2018	1. Burn 2. Burn/SD 3. Burn/PB 4. Burn/collagen 5. Burn/PB/collagen	*S. cerevisiae*	10^7 CFU/mL every 5 days for 22 day	PB/collagen had best wound healing measured numerous ways
Ong	2019	1. Wound/SA/ointment 2. Wound/SA/PB	*L. plantarum* protein rich fraction	10% in ointment	PB inhibited *S. aureus* growth, enhanced cytokines and chemokines, wound contraction, keratinocyte migration

Abbreviations: Abx, antibiotics; BSA, body surface area; BT, bacterial translocation; Glu, glutamine; IMG, Imiquimod; PA, *P. aeruginosa*; PB, probiotic; SA, *S. aureus*; SD, silver sulfadiazine.

positive wound-healing environment.[59-62] In contrast, topical insults are known to reduce AMP levels, thereby inhibiting wound healing.[63] However, some commensal bacterial strains are able to produce their own AMPs, which can influence the production of human AMPs and act synergistically in wound healing

TABLE 2 Probiotics in wound healing: Human studies

Author	Year	Type of study	Level of evidence	Probiotic used	Dose	Patient population	Control	Finding
Peral	2009	RCT	II	*L. plantarum*	10^5 daily to wound bed	Infected 2nd- and 3rd-degree burns, non-infected 3rd-degree burns	Silver sulfadiazine	1. Non-infected 3rd-degree: no impact 2. Infected 2nd-degree: as effective as SD-Ag in decreasing bacteria load, promoting granulation and healing 3. Infected 3rd-degree: likely significantly improved healing if larger sample size
Peral	2010	Pilot study	III	*L. plantarum*	10^5 daily to wound bed	Chronic venous ulcer	No control	PB reduced bacterial load, increased immune cells, modified inflammatory production, increased healing*Analysed cells from ulcer bed and compared with diabetics without ulcers and healthy subjects*
Zoccali	2016	Pilot	III	Probiotic derived active principles	Unknown	CO_2 laser	Historical controls	PB reduced erythema and oedema duration
Twetman	2018	RCT	II	*L. reuteri*	5×10^8 for 8 days BID prior and after in lozenge	Oral mucosa punch biopsy	Control lozenge	PB did not impact matrix metalloproteinases and interferons within 1 week
DiMarzio	1999	RCT	II	*S. thermophiles*	Unknown dose, 0.5 g, BID for 7 days	Non-pathologic	Lotion	PB increased skin ceramides
DiMarzio	2008	Pilot study	III	*S. thermophiles* BID	1.7 g/5 mL in 20 mL lotion BID	Elderly	Lotion	Increase in ceramides, hydration

Abbreviations: AD, atopic dermatitis; BSA, body surface area; LOS, length of stay; PB, probiotic; RCT, randomised control trial; SA, *S. aureus*.

and protective against pathogenic bacteria such as *S. aureus*[14,15,64-69].[70]

Topical probiotic therapy has been explored in animal and human models of cutaneous injury with the primary aim of reducing infection to augment healing. In animal thermal injury models, topical probiotics and kefir were able to decrease the production of inflammatory markers and associated septicaemia in infected wounds.[37,71] In an infected animal wound model, probiotics were able to enhance the immune response.[39] In human burn patients, topical probiotics were able to decrease the bacterial load as effectively as silver sulfadiazine, as well as result in a more favourable inflammatory response in patients with chronic venous ulcers[40,41] (Tables 1 and 2).

4 | WOUND HEALING AND TOPICAL PROBIOTIC: PREVENTION AND TREATMENT OF BIOFILMS

It is estimated that up to 80% of human infections, especially chronic wounds, are associated with biofilms and impaired healing.[72,73] Biofilm-associated cutaneous diseases include burns, pressure ulcers, surgical site infections, and diabetic foot ulcers. Studies have demonstrated that biofilms can include up to 20 genera of bacteria and 60 different subtypes.[57,74] Once a biofilm has formed, it is nearly impossible to eradicate because of increased resistance to systemic antimicrobial treatments. Biofilm resistance has been estimated to be 100 to 1000 times greater than planktonic bacteria.[75-77] When biofilms are exposed to sub-inhibitory antibiotic concentrations, or to the wrong antibiotics, mucoid phenotypes can develop, which generate thicker biofilms with additional matrix components, making eradication even more challenging.[78-80] Thus, topical and oral antibiotics are often ineffective and can actually worsen the infection as they are unable to attack the biofilm and inherently disrupt native, protective bacteria. *In vitro* studies have shown that, in biofilms, distinct species antagonism occurs between pathogenic and "commensal" species, highlighting the importance of beneficial bacteria.[18] It has been shown *in vitro* that the addition of probiotics to pathogenic bacterial cultures can inhibit the formation of biofilm development by pathogenic bacteria and fungi by about 50%.[81]

5 | WOUND HEALING AND TOPICAL PROBIOTIC: NON-PATHOLOGIC

Topical probiotics have also shown efficacy in healthy subjects. They were able to reduce the erythema and oedema associated with CO_2 laser therapy, reduce skin sensitivity in patients with reactive skin, and increase ceramide concentration and skin hydration.[82-85] However, not all studies investigating topical probiotics have demonstrated superiority compared with traditional interventions[43,44] (Table 2).

6 | CONCLUSION

Topical probiotics have demonstrated efficacy in multiple human and animal models at augmenting numerous aspects of wound healing, but there are many unanswered questions. There is marked heterogeneity regarding the insult investigated, type and dosing regimen of the probiotic utilized, and a lack of standardized outcome measures. We hope this review will stimulate the initiation of well-conducted prospective studies to determine the role that topical probiotics could play in allowing for efficient, safe, and reproducible wound healing, as well as prompt potential clinical trials.

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