Use of Probiotic Bacteria and Their Bioactive Compounds for Wound Care

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1 Introduction

Various commensal microbes start to inhabit the human body at birth and remain throughout one's existence. In comparison to harmful and infective microbes that can destroy the host barriers and cause disease pathogenesis, commensal microorganisms found in symbiotic communities are adapted for survival without sacrificing the integrity of the host (Thursby and Juge 2017; Lukic et al. 2017). Exploration of the human body and the functional integration and harmonization of microbiomes has shown that the microbiota has a vital influence on various biological functions like modulation of the immune system and fortification against infections (Lukic et al. 2017). The significance of commensal microbes in keeping up host well-being has been identified initially in gut microbiome investigation. The germ-free animals have been shown to be more susceptible to pathogen invasion (Kamada et al. 2012), have disrupted mucosal wound healing (Hernández-Chirlaque et al. 2016), and are more vulnerable to chemical poisoning (Breton et al. 2013). The methods that alter its composition to strengthen the physiological, immunological and metabolic functions of the host have become increasingly significant due to the major systemic and local consequences of the gut microbiome. This resulted in the discovery of advantageous microbial species (symbiotic) and increased host well-being. The lactic acid-producing microorganisms (*Lactobacillus* and *Bifidobacteria*) are among the most

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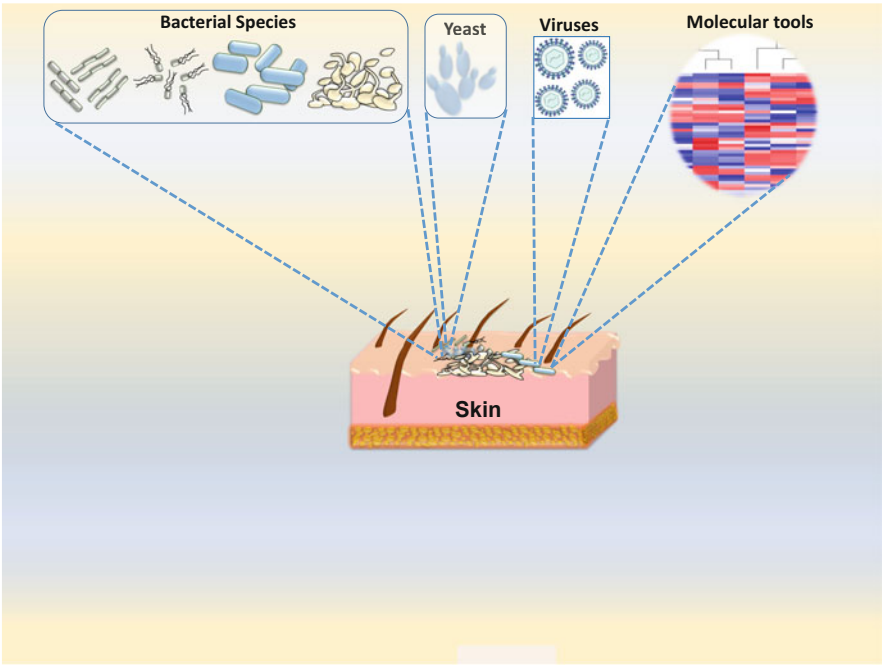

Fig. 1 Different inhabitants of skin microbiota

broadly investigated microbes, most often alluded to as probiotics, which have health benefits (Belkaid and Hand 2014).

The WHO (World Health Organization) has described the probiotic microbes as "live microbes that confer a health benefit on the host when administered in adequate amounts" (Mahajan and Singh 2014). These are live microbes (yeast or bacteria, predominantly, Fig. 1), the normal microbiome's members, which can equilibrate the human microflora and results in the predominance of advantageous microbes for the body (Tsiouris and Tsiouri 2017). These microorganisms help to reduce the level of low-density lipoproteins and contribute to down-regulate inflammation and the host's immune response (Hakansson and Molin 2011; Jones et al. 2012a; Wong et al. 2013). They are consumed as microbial food supplements. Different terms are used in the literature on nutrition for non-digestible fermented carbohydrates, which alter the gut microbiome (prebiotics) by endogenous bacteria, and combinations of probiotic microbes and prebiotics as synbiotics (Patel and Denning 2013). The probiotic microbes have been accounted for to be advantageous for treating or preventing various inflammatory cutaneous (skin) diseases (Hacini-Rachinel et al. 2009), respiratory tract infections (McFarland 2011), diabetes prevention and control (Rad et al. 2016), gastrointestinal (GI) disorders (Ringel-Kulka et al. 2011; Demers et al. 2014), ulcerative colitis (Abdin and Saeid 2008) and urogenital infections (Reid et al. 2001) to give some examples. Recent studies have also emphasized the use of non-viable compounds of probiotic microbes, known as

postbiotics, as a more stable probiotics alternative (Tsilingiri et al. 2012; Volz et al. 2014; Christensen and Brüggemann 2014). Postbiotics have gained significant importance in treating various disorders related to inflammation, where the utilization of live microbes carries the perils linked with excessive immune system activation.

The mode of action of microbes (probiotics) is attributed to their capability towards the immune response improvement, contend with harmful microorganisms for adherence at specific locations, antagonize the pathogenic microbes, and antimicrobial substance fabrication (Mahajan and Singh 2014). The probiotics' health benefits include prevention and treatment of several diseases and conditions such as lactose intolerance, gastrointestinal disorders, necrotizing colitis, irritable bowel syndrome, inflammatory bowel disease, allergies, numerous cancers, Upper respiratory infections, urogenital infections, Arthritis, AIDS, different oral health diseases such as prevention of dental caries, halitosis and periodontal diseases and many other effects which are under exploration (Mahajan and Singh 2014). The outcome of numerous clinical studies suggests that the probiotic microbes may use their advantageous effect for the treatment and prevention of various disorders to accomplish human well-being. The typical foods containing probiotics include kefir, yogurt, miso, sauerkraut (non-pasteurized), tempeh, sourdough bread, kimchi, and pickles (in brine, not vinegar), e.g. the *L. acidophilus* containing yogurt, which gives the yogurt, its valuable gastrointestinal health-related properties (Rezac et al. 2018).

The studies further suggest that some microbial probiotic strains and the mixture of probiotics such as a milk drink kefir (fermented) can have a positive influence on the wound repair process either by per os administration or topical application (Rodrigues et al. 2005; Huseini et al. 2012; Bourrie et al. 2016). The main reason for mortality and morbidity is impaired wound healing for a substantial portion of the population (Menke et al. 2007). Moreover, a higher degree of focus and research investigation is required to assess novel pharmaceutical compounds that can enhance wound healing and reduce the occurrence of chronic wounds and ulcers due to the substantial financial encumbrance and social influence of wound demands (Frykberg and Banks 2015). This book chapter reviews current information about probiotics on both GI epithelium and skin associated with their therapeutic properties. It also addresses their antimicrobial potential and identifies molecular and cellular mechanisms of action, suggesting innovative approaches to treating wound healing disorders.

2 Effect of Probiotics on Skin Microflora

The inherent microbiota flourishing within the gut of any individual is known to play an important role in gut-health, but what about our skin? Many millions of microbes live there, and during wound healing, the probiotic microbes may have enormous ability to prevent infections. The skin can serve as a physical barrier with numerous functions, e.g. thermoregulation, fluid homeostasis, metabolic and neurosensory

Table 1 List of different probiotic strains

Lactobacillus	***Bifidobacterium***	***Enterococcus***	***Lactococcus***	***Streptococcus***
L. acidophilus *L. casei* *L. brevis* *L. fermentum* *L. curvatus* *L. gasseri* *L. reuteri* *L. johnsonii* *L. rhamnosus* *L. salivarius* *L. plantarum*	*B. thermophilum* *B. animalis* *B. breve* *B. longum* *B. infantis* *B. adolescentis*	*E. faecium* *E. faecalis*	*L. lactis*	*S. thermophilus*
Propionibacterium	***Saccharomyces***	***Kluyveromyces***	***Leuconostoc***	***Pediococcus***
P. jensenii *P. freudenreichii*	*S. cerevisiae* *S. boulardii*	*K. lactis*	*L. mesenteroides*	*P. acidilactici*

Source: Lew and Liong (2013)

functions, immune responses and primary protection against infection as the skin's harsh environment prevents many microorganisms from inhabiting its surface (Romanovsky 2014; Sugiura et al. 2014). The skin contains two different kinds of microbe, i.e. resident and transient microbial strains (Table 1). The coagulase-negative *Staphylococci* (*S. epidermidis*), *Propionibacteria* (*P. avidum*, *P. acnes* and *P. granulosum*), *Bacillus* sp., *Acinetobacter*, *Micrococci*, and *Corynebacteria* are the most common resident species of skin. The transient microbial species include *E. coli*, *P. aeruginosa*, and *S. aureus*. The resident species are capable of establishing and reproducing the microbial colonies skin, thus offering an advantageous environment, while transient often refers to non-advantageous microbes which cannot produce colonies on the skin surface (Christensen and Brüggemann 2014).

In the competitive exclusion of antagonistic microbes that cause skin infection, skin processing proteins, sebum, and free fatty acids, the microbiota of the skin have a significant function. Intriguingly, the inhabitant microflora can be seen as "beneficial" to the healthy host but can be detrimental to the host with disrupted skin integrity (Cinque et al. 2011). The harmful microbes are preparing to advance into the body to colonize it at the point when the skin barrier is injured. This is especially perilous if the antibiotics-resistant harmful microbe in question causes significant harm to skin or other tissues (Cinque et al. 2011). Normally, *S. aureus* is present in the nose regions of about 30% of the population and generally does not cause skin damage. However, when the skin barrier is broken, *S. aureus* may result in serious infections. *S. aureus* is notorious for biofilms production, as soon as it occurs, the microbe appends to a surface, e.g. the sugar molecules and the skin create a matrix (protective) around the microbe. These films are generally antibiotic-resistant and are thus pose major health jeopardy (Kumar et al. 2020). *S. aureus* can cause sepsis when it spreads to the blood, the main cause of a child's death who has experienced serious burn injuries (Sakr et al. 2018). Another harmful microbe *P. aeruginosa*, also

identified to develop biofilms, is frequently present in infected wounds caused by burns. Normally present in a gut, this pathogenic microbe attacks and colonizes the skin, accompanied by other body organs, e.g. the lungs and liver in immune-compromised persons such as blistered patients by burns (Church et al. 2006).

The microorganisms may even cause atopic dermatitis (AD), rosacea, eczema, acne, and psoriasis. Although there are insufficient investigations following the probiotic's approach for the treatment of microbiota associated cutaneous diseases, it is fascinating to believe that usage of probiotic (topical) may be helpful for the prevention and/or treatment of microorganisms-related skin disease (Simmering and Breves 2009; Krutmann 2009). Significant evidence is also available in the prior art showing that probiotic microbes are effective for atopic dermatitis prevention, mostly in children during the post- and pre-natal periods (Martinelli et al. 2020). The controversial evidence remains, however, that the probiotic strains are successful in treating atopic dermatitis, and for this, further research is required. While presently not acknowledged as standard dermatological clinical procedures, some of the investigational studies are also there, indicating promising outcomes in wound healing, acne vulgaris, photo-protection with probiotics, and eczema treatment. While such outcomes are encouraging, more large-scale trials must be carried out before the incorporation of such treatment modalities into clinical practice (Rather et al. 2016).

Although the precise "probiotics-action" mechanism on the skin is not clear, it was proposed that microbial strains may produce a shielding barrier that averts overlaying malicious microbes (known as bacterial interference) from being detected by skin cells. Such an incidence can hinder the communication of Langerhans cells and keratinocytes with the immune system, thus avoiding an immune response (Fijan et al. 2019). It has likewise been noticed that antimicrobial properties of probiotics, such as antibiotics, may be used as alternatives to traditional therapies. In addition, the probiotics' immune-modulating effects help to reduce immune responses such as inflammation, redness and irritation (Lukic et al. 2017).

Stokes and Pillsbury conjectured a correlation in 1930 between an individual's stress or emotional state and stomach health, which further affects the well-being of the skin. They were well ahead of their time with their observations and hypothesis, and recent studies provide convincing proof of the correlation between these three different anatomical regions (Bowe and Logan 2011). A somewhat different approach to improving the skin's microbiota is done in the field of cosmetic treatments by topical treatment. A variety of items are available in the market, the majority of them are in the form of probiotic skin care creams. Although most research on the probiotics beneficial effects on the health status of skin have been performed through the oral administration, there is substantial proof that direct application on the skin is also a viable mode of treatment (Guéniche et al. 2008; Huseini et al. 2012). Future research could help to elucidate variations in the effectiveness of probiotics administered topically and orally. While antibiotics are used in wound care, the resistance to multiple drugs is widespread and infections persist. Various alternatives are being searched by scientists. Can microbes have much-needed strategies to avert infections that are life-threatening?

3 Fermented Probiotic Supernatant/Extract and Wound Healing

According to the theory of the gut–brain–skin axis, the use of probiotics modulates the microbiome that may have significant benefits on skin inflammation and skin homeostasis (Arck et al. 2010).

Increasing evidence suggests that microbial compounds, such as fragments of the cell wall, intra- and/or extra- cellular metabolites and even dead bacterial cells, can evoke some skin immune responses and improve the function of the skin barrier. Antimicrobial and immunomodulatory activities have been confirmed in extracts (cell-free) of lactic acid bacteria that have probiotic potential, indicating the use of probiotics in non-viable forms (Iordache et al. 2008). The alternative option may be natural cell components and metabolites in cases where the delivery of live cells is not feasible. In addition, at room temperature, cell metabolites and components are more stable than viable cells and are thus more acceptable for topical applications. Human clinical trials have shown that probiotics exert not only dermal benefits via the gastrointestinal pathway, but also via topical applications. By means of in vitro studies, Iordache et al. (2008) showed that the expression of soluble virulence factors by opportunistic dermal pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus* was inhibited by cell-free extracts of lactic acid bacteria with probiotic potentials such as *Lactobacillus plantarum*, *L. casei* and *Enterococcus faecium* and decreased their adherence ability to the cellular substrate represented by HeLa cells. Meanwhile, Guéniche et al. (2010) observed a statistically significant change after the use of cell lysate from *Bifidobacterium longum* sp. versus placebo in different inflammation-related parameters, such as a reduction in vasodilation, oedema, TNF-alpha release, and mast cell degranulation, using human skin explants (ex vivo) model. Three nanogel formulations consisting of probiotic supernatants (*Bacillus subtilis* sp. natto, *Lactobacillus reuteri* and *L. fermentum*) loaded chitosan nanogels have been prepared from the corresponding culture (Iordache et al. 2008).

The characterization of the chitosan nanogels was done previously by Zetasizer, FTIR and TEM. The efficacy and dressing activity of the prepared formulations were evaluated by examining wound closure and histological trials in Sprague-Dawley rats. The findings showed that all formulations of probiotic lysate had advantages over the mechanism of wound healing. Nevertheless, *Bacillus subtilis* natto has an enhanced wound healing rate, which is well understood in pathology research. It is suggested as a promising candidate for wound healing purposes by the favourable effects of probiotic lysate nanogels, including rational wound closing rate, good wound appearance, and adequate histological observation through in vivo analysis (Ashoori et al. 2020). Tsiouris et al. (2017) suggest that as a pharmacological treatment of wounds, sterile kefir extracts (70% kefir gel, *L. fermentum*, *L. brevis*, *L. reuteri*, *L. plantarum*) are more effective than the probiotic treatment of yeast (*S. boulardii*). While several studies and patents on the use of probiotic extracts for topical application on the skin have been published, the underlying mechanisms or the specific compounds responsible for the benefits of bacterial extracts on the skin

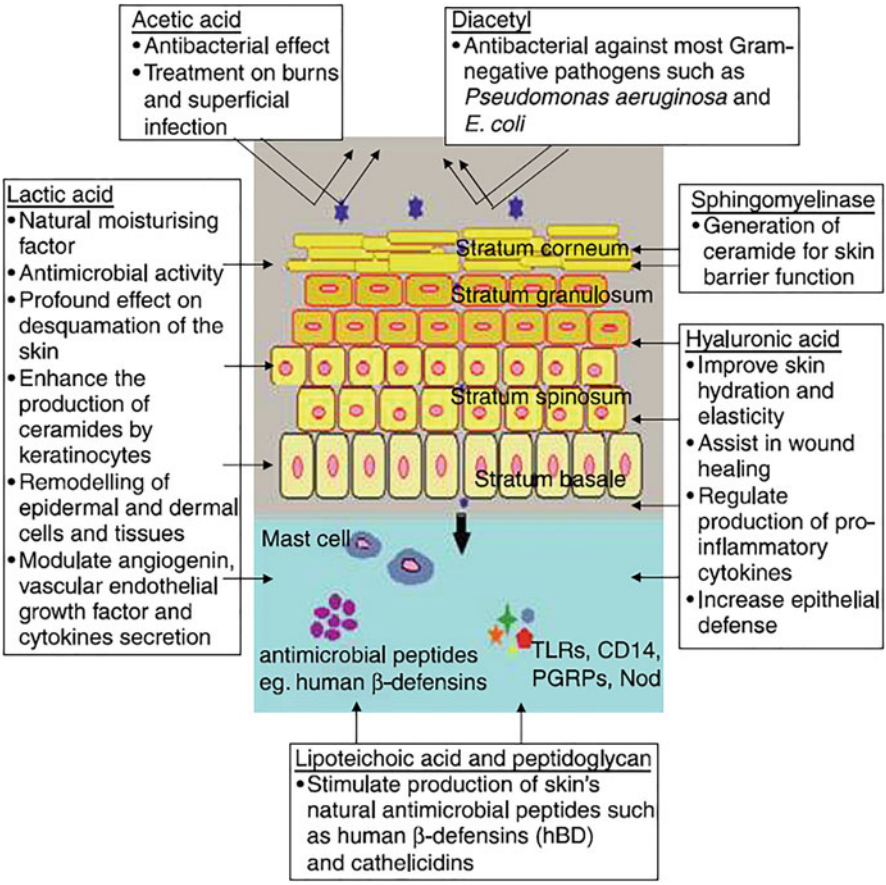

Fig. 2 Role of different bioactive compounds derived from probiotics in skincare (Source: Lew and Liong 2013)

remain unclear. The growing demand for probiotic dermal formulations further increases the need to understand the specific mechanisms of action. This chapter of the book is intended to report on the bacterial compounds that contribute to beneficial dermal effects and certain potential mechanisms of action of different bioactive compounds from probiotic supernatant or extract (Fig. 2).

4 Bioactive Compounds from Probiotics for Wound Healing

4.1 Hyaluronic Acid

The macromolecule hyaluronic acid is formed by polymerizing approximately 2000–25,000 repeating units of two sugar molecules, *N*-acetyl glucosamine and glucuronic acid (Chong et al. 2005). The hyaluronic acid's molecular weight, depending on the source, could range from 10^4 to 10^7 Da. In dermatology, hyaluronic acid has been used extensively as a biomaterial for stimulating wound healing and for bioengineering purposes. Besides, being utilized in cosmetic and dermatology goods, it is also broadly utilized in ophthalmology, drug delivery and pharmacology rheumatology (Kogan et al. 2007; Lew and Liong 2013). In most mammalian skin, hyaluronic acid is found to serve as a matrix. The hyaluronic acid is essential to preserve the structure of the standard stratum corneum and to maintain various epidermal barrier' functions. The hyaluronic acid also has a role in a number of other significant functions in the skin, e.g. in controlling cell proliferation, differentiation and tissue repair and in water immobilization in tissues. It also helps facilitate the water-soluble molecules and ion solutes transportation and retains the extracellular dermal matrix owing to its high-water binding ability. The hyaluronic acid is highly osmotic in nature that is significant for regulating tissue hydration during inflammatory processes (Weindl et al. 2004).

It has also been documented that by triggering β-defensin-2 via Toll-like receptors, the hyaluronic acid (low molecular weight) enhances epithelial protection (Gariboldi et al. 2008). β-Defensins, which are expressed in many body tissues, most remarkably epithelial surfaces and leukocytes, are the prevailing antimicrobial peptides involved in the host's response against bacterial infections (Menendez and Finlay 2007). Gariboldi et al. (2008) have stated that in all layers of the epidermal compartment, the low molecular weight hyaluronic acid treatment for murine skin enhanced mouse β-defensin-2 release.

It has been revealed by Taylor et al. (2004) that after injury, the fragments of hyaluronic acid are released, resulting in augmented chemokine IL-8 expression in the cells of the endothelium, thus stimulating the same to identify wound and initiate wound repair, while, during wound repair, the hyaluronic acid's antioxidant properties averted oxygen free radicals' damage on tissue granulation (Trabucchi et al. 2002). Moreover, the exogenous hyaluronic acid plays a supportive role in wound repairing due to its capability to retain moisture, thus promoting various physiological processes, e.g. provisional matrix's proteolytic degradation to facilitate epithelial migration, regeneration and remodelling (Chantre et al. 2019).

Commercially, Hyaluronic acid is obtained from rooster combs and few *Streptococcus* Group C (attenuated strains), which, as part of their capsule, naturally produce this compound. A detailed description has been documented of various sources from which hyaluronic acid can be extracted. It has been described that hyaluronic acid preparation from microbial sources contains very less contaminating

nucleotides, endotoxins and proteins, than those from animal sources (Shiedlin et al. 2004). In order to produce hyaluronic acid, very few microbial strains are known to date, e.g. *Pasteurella multocida* (Gram negative) and group A and group C streptococci (Gram positive). It was described for the first time in 2009 that hyaluronic acid is produced by *S. thermophilus* YIT2084 (a putative probiotic strain) in milk broth through fermentation (Izawa et al. 2009). *S. zooepidemicus* fermentations have also been reported to produce hyaluronic acid (low molecular weight, <200 kDa) under optimized fermentation conditions (Lew and Liong 2013). Recently, an alternative has emerged to produce higher hyaluronic acid yield by fermenting recombinant microbial strains that are Generally Recognized As Safe (GRAS).

4.2 Sphingomyelinase

Sphingomyelinase enzyme, from glucosylceramide and precursors of sphingomyelin, produces phosphorylcholine and ceramides for the extracellular lipid bilayers development in the stratum corneum (Slotte 2013). Its activity has been shown to be significant for skin barrier function (Bocheńska and Gabig-Cimińska 2020). A drop in stratum corneum' ceramide results in epidermal barrier dysfunction and water loss (Mizutani et al. 2009), including a deprivation of protection against bacteria and antigens. In addition, the reduced stratum corneum's ceramide levels have been advised as a potential contact dermatitis's aetiological factor, atopic dermatitis, irritant dermatitis and psoriasis (Murata et al. 1996; Berardesca et al. 2001). It is present in the interstices of stratum corneum and epidermal lamellar bodies and has been graded as the basis of their pH optima as neutral, acidic and alkaline sphingomyelinase. The soluble glycoprotein with an optimum activity at acidic pH (pH 5.0) is identified as the acidic sphingomyelinase. The neurological disorder Niemann–Pick syndrome resulted from the absence of this enzyme in humans. It was identified that persons suffering from Niemann–Pick syndrome also exhibited an aberration in the homeostasis of the permeability barrier of skin with very slow recovery kinetics resulting in acute disruption of the barrier (Lew and Liong 2013). Taking into account that acid Sphingomyelinase is contained in the outer part of the epidermis, the production of ceramides, the acid Sphingomyelinase is therefore responsible and further for basal permeability barrier functions. Moreover, the skin ageing has been related to a reduction in inner epidermal acid Sphingomyelinase (Jensen et al. 2005). The neutral sphingomyelinase, on the other hand, is associated with the cell membrane and, during permeability barrier repair, is significant for cell signalling through increased ceramide accumulation (Kreder et al. 1999). In aged skin, the decreased neutral Sphingomyelinase activity in the outer and inner epidermal layers was found (Lew and Liong 2013), possibly due to decreased proliferation rates, resulting in decreased barrier repair capacity. Mice deficient in TNF-induced neutral Sphingomyelinase activation indicated a smaller increase in epidermal proliferation upon barrier disruption and abridged barrier repair capacity (Kreder et al. 1999). The neutral

Sphingomyelinase activities in lesional and non-lesional atopic dermatitis skin were also reported to be reduced, linked with impaired keratins expression and cornified envelope proteins, which are vital for skin barrier functions (Lew and Liong 2013).

Sphingomyelinase is found in mammalian cells and various microbes (bacteria and yeast), with large Sphingomyelinase activity variations among different microbial strains. The microbial Sphingomyelinase is a secretory protein released into the media from cells, whereas mammalian neutral Sphingomyelinase is a membrane-bound protein (Di Marzio et al. 2001). The alkaline sphingomyelinase can be extracted from probiotic microbes and is an enzyme located exclusively in the intestinal brush border and bile that hydrolyses sphingomyelin into sphingosine, sphingosine-1-phosphate and ceramide, contributing to apoptosis of epithelial cells. In premalignant and malignant intestinal epithelia and in ulcerative colitis tissues, decreased levels of alkaline sphingomyelinase have been identified (Soo et al. 2008). Reduced alkaline sphingomyelinase levels have been observed in premalignant and malignant epithelial and ulcerative colitis tissues (Soo et al. 2008).

4.3 Lipoteichoic Acid

One of the immune-stimulating structural constituents of both non-pathogenic and pathogenic Gram-positive bacterial cell walls is called lipoteichoic acid that has very critical role in bacterial growth and physiology (Villéger et al. 2014). Prior investigations revealed that Lipoteichoic acid could serve as a major pathogen-associated molecular pattern, resulting in nitric oxide (NO), activation of NF-κB (nuclear transcription factor), pro-inflammatory cytokines and other pro-inflammatory mediators' production (Kao et al. 2005; Lebeer et al. 2012). An infection or injury in the host's body is followed by the inflammatory reaction to restore and preserve homeostasis. The lipoteichoic acid from *S. aureus* (a pathogenic Gram-positive bacteria) may, however, induce chronic inflammation and resulting in septic shock, an example of systemic inflammatory response syndrome development (Lew and Liong 2013). The structure-activity correlation investigations of lipoteichoic acid revealed that important strain-specific variations may occur, although, most lipoteichoic acid molecules have a similar basic structure. Unlike Lipoteichoic acid from *S. aureus*, Lew and Liong (2013) isolated lipoteichoic acid from beneficial probiotics, e.g. *L. plantarum* that induced tolerance by protection against the pro-inflammatory cytokines production associated with TNF-α sepsis.

Lipoteichoic acid has been found to promote skin protection against microbial infections through toll-like-receptor induction upon topical application (Sumikawa et al. 2006). In the cutaneous pathogen recognition system, the toll-like receptor activation initiates the release of antimicrobial peptides (soluble effectors) that maintain dermis sterility (Lai et al. 2010). The most popular forms of antimicrobial peptides that contribute against skin bacterial infections, in the host response are human β-defensins and cathelicidins. Various *Lactobacilli* and *Bifidobacteria* species have adequate amounts of Lipoteichoic acid to upsurge dermal cellular defence

against microbial infection (Lew and Liong 2013). Lipoteichoic acid also contributed to cutaneous wound healing by activating human β-defensins, in addition to the antimicrobial properties, and accomplished a number of immune-modulatory functions, performing not only as pro-inflammatory agents but also as a main connexion between the adaptive and the innate immune system (Diamond et al. 2009).

4.4 Peptidoglycan

The polymerization of *N*-acetylmuramic acids and *β*(1–4)-linked *N*-acetylglucosamine, cross-linked by short peptides containing alternating D- and L-amino acids produce peptidoglycan (PG) that is considered as the main structural constituent of microbial cell wall responsible for upholding the shape and to provide shield against osmotic lysis (Dziarski 2003). Peptidoglycans are particularly copious in Gram-positive bacterial strains, where it accounts for around 90% of the cell wall's weight and thickness up to 80 nm (Lew and Liong 2013). On the other hand, the cytoplasmic membrane under the lipopolysaccharide-containing outer membrane of Gram-negative bacteria is surrounded by a relatively thin layer of peptidoglycan (thickness < 10 nm). Although the structure and development of the peptidoglycans are amazingly preserved across bacterial species, it has been found that the chain lengths depend on the bacterial species and various conditions of growth (Lew and Liong 2013).

By stimulating the innate immunity system through Toll-like receptor 2, the peptidoglycan plays a crucial role in the skin's protection against pathogenic microbes resulting in the secretion of numerous chemokines and cytokines that are involved in immune responses (Niebuhr et al. 2010). It has also been demonstrated that the peptidoglycan has the capability to activate NF-kB (nuclear factor) and triggers the interleukin-8 production abundantly from keratinocytes, indicating that peptidoglycan plays a vital role in the chemokines and cytokines production from keratinocytes (Matsubara et al. 2004). Numerous other peptidoglycan recognition molecules also recognize the peptidoglycan, including the nucleotide oligomerization domain-containing proteins (CD14), peptidoglycan lytic enzymes (lysozyme and amidase) and a family of Peptidoglycan recognition proteins (PGRPs, Dziarski 2003; Kumar et al. 2010). These molecules induce the responses of the host to microbes, mediate the antimicrobial peptides or degrade Peptidoglycan and chemokines release that results in recruitment of phagocytic cells to the site of infection (Dziarski and Gupta 2005; Lew and Liong 2013). The microbe-derived molecules like peptidoglycan have been reported to be able to induce or increase the expression of human β-defensins in whole skin keratinocytes of the humans, contributing to the stimulation of host's innate immunity (Sørensen et al. 2005). *Lactobacilli* peptidoglycan stimulates innate immune response through Toll-Like Receptor 2 and also to increases the IL-12 production and other regulatory factors by macrophages, which further results in skin protection (Paradis-Bleau et al. 2007; Lew and Liong 2013).

4.5 Lactic Acid

Lactic acid is an organic acid, classified as one of the α-hydroxy acids, with one hydroxyl group attached to the alpha position of the acid and produced by microbial fermentation or chemical synthesis. The lactic acid produced by chemical synthesis mostly consists of the racemic mixture (DL-lactic acid), while L(+)- or D(−)-lactic acid (optically pure) can be derived through fermentation using appropriate microorganisms (Wee et al. 2006; Tang and Yang 2018). At sufficient concentrations, *Lactobacilli* strains may produce lactic acid to show antibacterial activity against the majority of the pathogenic microbes on the skin (Lew et al. 2013). They metabolize carbohydrates with at least 50–85% lactic acid, either homo-fermentatively or hetero-fermentatively, for production of the main end product, i.e. lactic acid (Yeo and Liong 2010). Lactic acid has been extensively utilized for a long time in skin care products and cosmetic regiments, e.g. exfoliants, moisturizers and emollients (Smith 1996). One of the causes that lactic acid (α-hydroxy acids) is frequently used as a chemical peeling agent and an exfoliator is because of its profound effect on skin desquamation. The induction of skin desquamation is done by the dissociation of the cellular adhesions, which occurs via the chelating action of α-hydroxy acids as a result of reduced concentration of epidermal calcium ions. The reduced epidermal calcium ion level also tends to promote cell growth and delays cell differentiation, resulting in younger-looking skin (Soleymani et al. 2018). Moreover, due to its ability to boost the function of the stratum corneum barrier, it has the potentials for various skin applications and also improves the ceramide's production by keratinocytes. The improved ceramide 1-linoleate to oleate ratio has a significant role in enhancing the functions of the skin barrier (Yamamoto et al. 2006). Pasricha et al. (1979) have investigated lactic acid's antimicrobial activity against dermal pathogens, e.g. beta haemolytic *Streptococci*, *S. aureus*, *Proteus* species, *E. coli* and *P. aeruginosa*. Owing to its non-toxic and non-sensitizing properties, the long-lasting topical use of lactic acid cream has been suggested as a preventive remedy for acne vulgaris, in addition to its antimicrobial activity.

4.6 Acetic Acid

Acetic acid is produced both chemically and by microbial fermentation at industrial level. Heterofermentative lactic acid bacteria can produce acetic acid via the hexose monophosphate or pentose pathway (Yeo and Liong 2010). The acetic acid usage has been described from time to time as a topical agent in the treatment of microbial infections and also been used to treat superficial infections and burns. When several antibiotic-resistant strains cause infection and where therapeutic options are insufficient, it has been suggested as the best remedy (Nagoba et al. 2008). It has been shown that acetic acid exerts antibacterial effects on several microbes, including *S. aureus* and *P. aeruginosa* (Lew and Liong 2013).

4.7 Diacetyl

Some strains of the genera *Streptococcus*, *Leuconostoc*, *Lactobacillus* and *Pediococcus* can produce diacetyl, also referred to as 2,3-butanedione. *Lactobacilli* and *Bifidobacteria* strains might produce diacetyl (concentrations up to 30 mg ml^{-1} s), signifying their possibility for antimicrobial dermal activities with maximum sensitivity compared to Gram-positive bacteria against Gram-negative bacteria and fungi (Lew et al. 2013). Although the majority of the Gram-negative bacteria, e.g. *Bartonella* sp. *Borrelia burgdorferi*, *P. aeruginosa*, *Pasteurella multocida*, *Vibrio vulnificus*, *Klebsiella rhinoscleromatis*, *Helicobacter pylori* and *S. typhi*, are not typical skin microflora residents, it has been suggested that they cause cutaneous infections. Diacetyl, at a very low concentration of 100 ppm, has been proved to be bactericidal against *E. coli* and *S. aureus* (Lanciotti et al. 2003). A pathogen *S. aureus* has appeared as a major infectious microbe of skin and soft tissue, including cellulitis, folliculitis and impetigo (Miller and Cho 2011), and one of the most common skin pathogens identified is *E. coli* (Doern et al. 1999). The diacetyl's antimicrobial activity has been well acknowledged, but, there is very little research available on topical application of diacetyl and considerable investigations are needed to establish its effects on the skin and other tissues.

4.8 Antimicrobial Substances

The growing attention has been given to the possible topical application of probiotic microbial strains' ability to produce potent antimicrobial toxins (i.e. H_2O_2, organic acids, bacteriocins and bacteriocin-like substances) to effectively avert pathogen adhesion and outcompete undesired microorganisms (Fig. 3) (Gillor et al. 2008; Cinque et al. 2011). The compositions comprising probiotic microbes, spores and their products, have been described by Farmer (2005), apposite for topical usage on the skin, can be utilized to impede the growth of microbes and combinations thereof. Different treatment approaches and therapeutic systems to prevent the growth of pathogens and combinations thereof through topical application of pharmaceutical compositions, comprising of isolated species of *Bacillus*, spores or an extracellular product of *B. coagulans* (a supernatant or filtrate of a fermented *B. coagulans* culture) are also disclosed in the invention.

Spigelman and Ross (2008) have also given a composition and method for the probiotic microorganisms' application to skin surfaces to avert or constrain pathogenic microorganisms' contamination. The probiotic microorganisms include bacteria, yeast or fungi. The appropriate probiotics should be selected on the basis of one or more unique characteristics, the desired characteristics being the competitive exclusion of pathogenic microbes from the surface to which they are applied, antibiotic sensitivity, human tissue adherence, a high resistance to oxygen and acid and antimicrobial activity. More specifically, the procedure consists of multiple

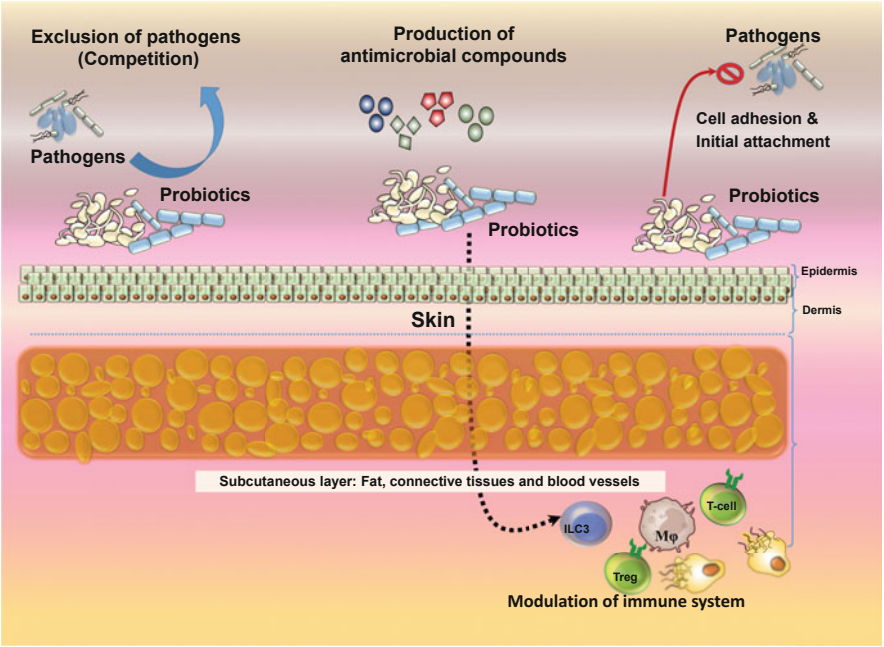

Fig. 3 Demonstration of potential mechanisms of action of probiotics' antagonistic effects

methods of application (e.g. wiping paper, spraying and lotions) of one or more probiotic microbes to a wide range of surfaces (e.g. hospital equipment, fixtures and human skin), effectively avoiding, at least partially, their infection, invasion, growth and cross-contamination by pathogenic microorganisms.

The technique depends on the probiotic's capability to produce isolated colonies to generate a protective layer that can prevent and eliminate pathogenic microbes unable to survive on top of other bacteria. Depending on various factors such as the therapeutically effective amount, type, probiotic application mode or the degree of contamination of the biological or non-biological surface, the probiotic application is recommended for a suitable period. The method, therefore, suggests the usage of a single or a multitude of diverse probiotic microbes, serially adding multiple layers of bacteria to combat single or many resistant kinds of pathogenic microorganisms. Numerous lactic acid bacterial species producing a number of bacteriocins, including *Lactobacillus*, *Pediococcus*, *Lactococcus*, *Leuconostoc*, *Carnobacterium* and *Propionibacterium* have been reported in relation to the potential use of bacteriocin-producing strains as probiotic and bio-protective agents (Mokoena 2017). *Lactococcus* sp. HY 449 bacteriocin was capable of preventing the growth of skin inflammatory bacteria, e.g. *S. epidermidis*, *S. aureus*, *P. acnes* and *Streptococcus pyogenes* (Oh et al. 2006). The bacteriocin's inhibitory effect used in the research work done by Oh et al. (2006) was triggered by the bacteriolytic activity on the cell membranes and cell walls of *P. acnes*. Acknowledgments to its antimicrobial

properties, bacteriocin from *Lactococcus* can be used for many purposes in cosmetic applications.

The eubiotic product, according to Teodorescu (1999), is a mixture of three probiotic *Lactobacillus acidophilus* LR, LV and LD strains, the association in the mixture in equivalent parts before lyophilization, for the treatment and maintenance of tegument. In order to abolish pathogenic microflora and to be immune to cosmetic composition, this eubiotic substance is capable of preserving the skin pH at physiological values.

4.9 β-Defensins

Lactobacillus extracts can induce dose-dependent β-defensins production in skin cells, which may be useful in reducing or preventing the growth of skin microbial populaces (Sullivan et al. 2009). The effective quantity of *Lactobacillus* extract is applied to a skin wound or an open cut that may have been in direct contact with soil or unwanted microbes on a chronic basis, added to clean skin to uphold a hale and hearty skin flora. These extracts can also be beneficial in treating acne. Indeed, when applied consistently over a 2-month span, the *L. plantarum* extract containing topical compositions/lotions is shown to lessen the occurrence of both inflamed and non-inflamed acne lesions.

Furthermore, the extracts were used as a preservative in cosmetic or pharmaceutical items, especially *L. plantarum*, which has a wide range of activity against Gram-negative and Gram-positive bacteria. Acne vulgaris is a multifactorial disorder characterized by *P. acnes* hyper-colonization, inflammation and immune responses. In an in vivo study, the synbiotic capability of Konjac glucomannan hydrolysates and probiotic bacteria to inhibit *P. acnes* growth has recently been reported, indicating that it may be promising to develop a new probiotic therapy alternative to minimize the acne episodes (Cinque et al. 2011).

5 Probiotics, Infections and Intestinal Wound Healing

In antimicrobial treatment of pathogens, the close association of lactic acid bacteria and *Bifidobacteria* with epithelial cells makes them ideal probiotic candidates (Lukic et al. 2017). Lactic acid bacteria and *Bifidobacteria* use their interaction with gut epithelial cells to hinder pathogens' growth directly and capability to enhance tissue repair mechanisms and host mucosal defence systems. In combating overt and opportunistic pathogens, these properties are of paramount importance.

5.1 Probiotics: Direct Inhibition of Pathogens' Growth

The antimicrobials' production, pathogens displacement from mucus and epithelial cells, removal of pathogens by co-aggregation and quorum quenching are recommended direct probiotic action mechanisms against pathogens. The organic acids, H_2O_2, reuterin, diacetyl and bacteriocins are the antimicrobials produced by probiotic strains. The anti-pathogenic activity against Gram-negative pathogens is essentially due to the production of organic acids by numerous probiotic strains, from both lactic acid bacteria and *Bifidobacteria* (Piqué et al. 2019). Hydrogen peroxide producing *Lactobacilli* (*L. jensenii*, *L. fermentum* and *L. acidophilus*) have been associated with abridged count of Gram-positive bacteria (fastidious anaerobe), including *Prevotella*, *Bacteroides*, *Mycoplasma* sp. and *Gardnerella* (Atassi et al. 2006; Breshears et al. 2015). *L. reuteri* produced a well-known antimicrobial metabolite Reuterin (3-hydroxypropionaldehyde) and thought to exert its influence through the thiol groups' oxidation in the target pathogenic microorganisms (Schaefer et al. 2010). Importantly, without killing beneficial microorganisms, reuterine will precisely inhibit the growth of harmful gut bacteria, causing *L. Reuteri* to kill gut invaders while keeping the microbiota of the natural gut intact. Reuterin also exhibits antimicrobial activity against the common chronic wound pathogen, *Staphylococcus* (Arqués et al. 2008). Diacetyl is produced by *Lactobacilli*, another metabolic product that also shows a broad range of antimicrobial ability against Gram-negative and Gram-positive pathogens (Kang and Fung 1999; Langa et al. 2014).

Bacteriocins, the second class of metabolites from probiotic strains, are very small peptides by microbes that display a wide spectrum of antimicrobial activity both in vitro and in vivo (Minami et al. 2009). *S. salivarius*, (producing bacteriocin), a commensal of oral epithelium, is a potential inhibitor of *S. pyogenes* (a pathogen) triggers pharyngitis and cutaneous infections (Heng et al. 2011). Both in adults and children, *S. salivarius*'s prophylactic oral administration has shown beneficial effects in preventing recurrent infections of *S. pyogenes* (Di Pierro et al. 2013).

The potential of auto-aggregation by several microbial strains (probiotics), including *Bifidobacterium longum*, *L. delbrueckii* and *L. rhamnosus*, confer the antimicrobial ability to co-aggregate with other microorganisms that include the common wound pathogens *Candida albicans* and *S. aureus* (Barzegari et al. 2020). In addition to co-aggregation and antimicrobial metabolites' production, probiotic microbes can move intestinal pathogens from the epithelium of the gut or stomach. The specific surface molecules obtained from *Lactobacilli* (extracellular polysaccharides) have the ability of displacement, which further allow *L. paracasei* to competitively adhere to gut epithelial cells and displace the harmful microbes (Rutherford and Bassler 2012).

The inhibition of harmful microbes' quorum sensing (QS) system is another emerging antimicrobial mechanism of lactic acid-producing microbes. Quorum sensing refers to an intercellular communication mechanism that microorganisms use to modify cell-population density-based gene expression to form biofilm and

confer virulence (Pastar et al. 2013; Kumar et al. 2020). Majority of the pathogens, including microbes usually found in chronic wound infections (e.g. *P. aeruginosa* and *S. aureus*), use quorum sensing for resistance to host defence, virulence and biofilm formation (Lukic et al. 2017). Nevertheless, probiotics can interfere with the quorum sensing of pathogens. Specifically, *L. plantarum* has been shown to prevent the quorum sensing signalling molecules (acyl-homoserine-lactone) production by *P. aeruginosa*, along with the decrease in the formation of biofilm (Valdez et al. 2005).

5.2 Epithelial Barrier and Probiotic Effects

The probiotics can enhance the epithelial barrier's function, thereby limiting pathogen invasion, besides direct antimicrobial effects on harmful microorganisms, (Ohland and MacNaughton 2010). By improving expression and controlling the localization of tight junction proteins both in vivo (Karczewski et al. 2010) and in vitro (Anderson et al. 2010), they have a well-defined function in strengthening the gastrointestinal barrier, e.g. increased occludin, claudin and zonula occludens 1 expression in the gut in newborn piglets resulting from oral administration of *L. reuteri* (Yang et al. 2015). In the same way, following oral administration of *L. plantarum*, occludins and zonula occludens 1 were recruited to the tight junction region (Karczewski et al. 2010). Additionally, a mixture of eight distinct probiotic bacterial strains stimulates the suppression of chronic inflammation by epithelial barrier function fortification, which have been shown in the murine models of chronic ileitis (Ewaschuk et al. 2008).

In addition to *Lactobacilli*, the probiotic strain belonging to genus *Bifidobacterium* has also shown similar effects. The expression and trans-epithelial resistance of tight junction proteins occluding and zonula occludens 1 were increased by *B. infantis* in human gut epithelia. Improved trans-epithelial resistance has also been correlated with enhanced cell signalling events significant for extracellular signal-regulated kinases phosphorylation, barrier formation and p38 (Fijan et al. 2019). In order to verify the effects of probiotics on wound healing in the gastrointestinal tract, various experimental models, including acetic acid-induced ulcers, full thickness wounds and intestinal anastomoses, have been extensively examined. The beneficial effects of *Lactobacilli* in these studies were largely mediated by stimulation and activation of fibroblast proliferation and/or migration by the epithelial cells (Lukic et al. 2017).

Aside from improving the epithelium repair, the presence of *L. plantarum* has been shown to linked with increased production of collagen in the intestine (Nasrabadi et al. 2011), and similar skin effects have been shown in hairless mouse model with UVB induced skin photo-ageing after oral administration of *L. acidophilus* (Lukic et al. 2017). Given that the chemokines, cytokines and growth factors have regulated the epithelial cells' and fibroblasts' functions (Pastar et al. 2014), the epidermal barrier fortification by probiotics is closely linked with their

impact on immune components. Probiotics also have an effect on innate immune components of the intestinal barrier by inducing β-defensin, which is known to promote wound healing in addition to its function in fighting intestinal pathogens (Lukic et al. 2017).

In vivo murine studies have revealed that commercially available probiotic microbial mixture can be utilized for the stimulation of the vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF β) expressions (Dharmani et al. 2013), while *Saccharomyces boulardii* containing probiotic formulation was shown to stimulate insulin-like growth factor (IGF), epidermal growth factor (EGF) and its receptor activity (EGFR) (Fordjour et al. 2010). Additionally, *L. rhamnosus* has been reported to stimulate hypoxia-inducible factor 2α (a master controller of progenitor stem cell recruitment during tissue repair) in vivo (Wang et al. 2011).

6 Chronic Wounds and Probiotic Therapy

Considering the potential role of skin microbiota and biofilms in skin-related diseases, the investigators have begun to investigate probiotics for the chronic wounds' treatment e.g. kefir extracts (natural probiotic compounds) containing topical gels have been applied to infected burn wounds in rats and have shown improved collagen formation and epithelialization compared to controls treated with silver sulfadiazine (Lukic et al. 2017). The probiotics administered to mice (orally) were able to modulate interleukin-10 levels and skin immune cell density after an injury caused by UV radiation, indicating that these beneficial microbes in cutaneous tissues can exert strong immune-modulatory effects (Guéniche et al. 2006). The investigators have also isolated microbes from burn wounds and demonstrated that most of the microbial strains were extremely vulnerable to *L. acidophilus* (Jebur 2010). Via competitive inhibition of pathogenic microbe *P. aeruginosa* and disruption of bacteria–bacteria communication pathways, i.e. quorum sensing, *L. plantarum* has a potential role in the topical treatment of wounds (Peral et al. 2009). Some of the useful tools for reconstructive surgery include bio-prostheses and implants, but they are at greater risk for formation of biofilm and chronic infection. Therapies based on probiotics can play a role in reducing these complications, e.g., surfactants obtained from probiotics have been shown in a voice prosthesis model to lessen pathogenic microbial colonization and extend graft function (Rodrigues et al. 2004). Some probiotic strains are capable of producing oxidative reactions that impede the growth of fungi and the formation of biofilms (Reid et al. 2006). These impacts may be due to pathogenic microbial adhesion changes and can also be used prophylactically in high-risk patients. However, in clinical environments such as infected (contaminated) mesh, contracture or extrusion for the breast implant, and other prosthetic complications, the use of probiotics remains unproven but is considered as a field of considerable research potential (Wong et al. 2013).

Some experiments have revealed the feasibility of manipulating microbial properties to facilitate wound healing through the application of principles in tissue engineering, e.g., investigators have produced a topical patch containing nitric oxide producing probiotics (e.g. lactic acid bacteria), a molecule well recognized to enhance the synthesis of fibroblast collagen and increase tissue blood flow (Isenberg et al. 2005). This bacteria-impregnated patch substantially improved wound closure in infected and ischemic wounds in rabbits measured after 3 weeks (Jones et al. 2012b). Further, investigations are needed in order to understand the probiotics' role and possible delivery mechanisms for non-healing wounds. In conjunction with traditional approaches to wound healing, probiotic-based therapies could be a significant adjunct for potential paradigms of wound treatment. The genetically modified microorganisms or engineered microbial by-products may play a role in regulating interactions of host-bacteria or bacteria–bacteria to facilitate the repair of cutaneous tissue in addition to the exogenously administered probiotic strains.

7 Probiotics and Cutaneous Wound Healing

Bifidobacteria and *Lactobacilli* are the most widely studied potential probiotics for numerous dermatological conditions, including non-healing wounds (Baquerizo Nole et al. 2014). The protective abilities of probiotic microbes against skin pathogens have been demonstrated in numerous in vitro experiments with human keratinocytes (Lukic et al. 2017). The probiotic strains, *L. rhamnosus* and *B. longum*, similar to their impact on the gut epithelium, have been shown to mend tight junction functions and expression of zonula occludens 1, claudin 1 and occludin in *S. aureus* infected keratinocytes (Sultana et al. 2013). Unlike *L. rhamnosus*, *B. longum* augmented the claudin 4 expression, another major tight junction protein (Sultana et al. 2013), proposing that *B. longum* can affect tight junction function through a substitute mechanism by lessening para-cellular permeability and therefore averting the pathogen invasion.

Furthermore, the Toll-like Receptor 2 activation increases the tight barrier function in keratinocytes as well as gut epithelial cells (Yuki et al. 2011). *B. longum*'s modulation related to functions of tight junction seems to be Toll-like Receptor 2 dependent as tight junction protein levels and trans-epithelial electrical resistance cease to upsurge when Toll-like Receptor 2 is neutralized or blocked, respectively (Sultana et al. 2013). The implications of the commonly used *L. rhamnosus*, on the other hand, on keratinocytes are Toll-like Receptor 2-independent, indicating that this probiotic species utilizes another method to augment tight barrier function (Sultana et al. 2013). The mitogen-activated protein kinase pathway, known to increase tight barrier function through modulation of extracellular signal-regulated kinases and p38 (Lukic et al. 2017), is a possible pathway involved in this process (Lukic et al. 2017).

The probiotic species (*L. plantarum* and *L. reuteri*) also possess the capability to upsurge tight barrier function in primary human keratinocytes (Sultana et al. 2013). *L. rhamnosus* and *L. reuteri* also improve re-epithelialization through enhanced keratinocyte migration and cellular proliferation (Mohammed et al. 2015). The probiotics are also able to cause re-epithelialization through chemokines induction, e.g. *L. rhamnosus* augmented the chemokine CXCL2 and its receptor CXCR2 expressions that stimulates proliferation and migration of keratinocyte during normal wound healing (Mohammed et al. 2015). Although the majority of probiotic microbes have been advantageous for function associated with keratinocyte, *L. fermentum* deceases viability of keratinocyte and re-epithelialization (Mohammed et al. 2015; Lukic et al. 2017), demonstrating strain-specific effects once again.

The antibacterial activities of already established probiotics, e.g. reduction of pathogen adhesion and inhibition of pathogen growth, are the methods of fortification against cutaneous wound infections. The protective effect exhibited by *L. rhamnosus* by *S. aureus* growth inhibition in infected keratinocytes is yet unknown mechanism (Mohammedsaeed et al. 2014). The probiotics like *L. rhamnosus* and *L. casei* Shirota exhibited antimicrobial activity that is not due to acid (Mohammedsaeed et al. 2014), hydrogen peroxide or bacteriocin production (Vesterlund et al. 2004), featuring a number of protective mechanisms by probiotics. Additionally, *L. plantarum* extract, by interfering with its quorum sensing system, disrupt *P. aeruginosa*'s pathogenic characteristics, a widespread chronic wound pathogen. Through inhibition of *P. aeruginosa* virulence factors pyocyanin, elastase and rhamnolipid, this extract without live probiotics was able to reduce biofilm growth and bacterial adhesions (Ramos et al. 2012).

Lactobacilli can also, by competitive exclusion, inhibit pathogen invasion into keratinocytes. *L. rhamnosus* and *L. reuteri* are capable to impede the initial *S. aureus* adhesion to keratinocytes and displace already attached *S. aureus* to human keratinocytes (Mohammedsaeed et al. 2014; Lukic et al. 2017). The pertinent molecules that contribute in *S. aureus* exclusion and displacement from keratinocytes derived from human are still unidentified, but they depend on moonlight proteins: a class of multi-functional bacterial adhesins that may, among many functions, bind to epithelial cells (Kainulainen and Korhonen 2014). The enolase from *L. crispatus*, an example of a moonlight protein, can bind to collagen-I and laminin (Antikainen et al. 2002), while *L. plantarum* enolase binds to fibronectin and avert *S. aureus* adhesion to epithelial cells (Castaldo et al. 2009). A mechanism for displacement, as illustrated by *L. rhamnosus*, will enable probiotics not only to protect keratinocytes from infection but also to rescue them, both of which are important features for potential clinical applications. The supernatants, lysates and metabolites from probiotic microorganisms have been extensively investigated in vivo and in vitro to address protection of utilizing live probiotic bacteria topically, showing beneficial effects similar to live microorganisms (Mohammedsaeed et al. 2014; Lukic et al. 2017).

In vivo wound repair investigations were mainly focused on topical application of probiotics that support in vitro data, showing enhanced wound repair via increased tissue repair and reduced bacterial load in rodent wound models (Rodrigues et al.

2005). *L. plantarum* (topical application) inhibited colonization of wounds caused by *P. aeruginosa* in a mouse model with burns by clearing *Pseudomonas* from the liver, spleen and skin, via lessening apoptosis and increasing phagocytosis and (Valdez et al. 2005). Even the use of kefir (mixture of lactic acid bacteria and yeasts) has resulted in improved healing with antifungal and antibacterial effects (Lukic et al. 2017).

L. plantarum (topical use) has interfered with pathogen colonization caused by *S. aureus*, *S. epidermidis* and *P. aeruginosa* in human burn wounds (Peral et al. 2009). Topically applied *L. plantarum* Treatment with lessened bacterial load and encouraged wound repair is found to be comparable with silver sulfadiazine treatment. One possible mechanism underlying *L. plantarum*'s antimicrobial/anti-pathogenic characteristics is that *P. aeruginosa* and *L. plantarum* stimulate reverse effects on the infection (Hessle et al. 2000). *L. plantarum* (Gram-positive bacteria) activates the secretion of interleukin-12, which activates natural killer cells and cytotoxic T cells to secrete IFNγ, while Gram-negative pathogen *P. aeruginosa* favourably stimulates interleukin −10, which prevents those functions (Hessle et al. 2000). The antagonistic inflammatory response regulation, however, does not account for antibacterial effects of *L. plantarum* on *S. aureus*, a Gram-positive pathogen. Topical use of *L. plantarum* also boosted wound healing in human chronic venous ulcers (Peral et al. 2010) infected predominantly with *P. aeruginosa* and *S. aureus*, stimulated a continuous process of healing that decreased microbial load and triggered the granulation tissue formation (Peral et al. 2010; Lukic et al. 2017). Polymorphonuclear cells screened from the ulcer bed showed augmented interleukin-8 production, decreased apoptosis percentage and necrosis upon *L. plantarum* treatment. Taking its antimicrobial and immunomodulatory effects in humans into account, *L. plantarum*, by controlling interleukin-8 levels and controlling the entry and activity of Polymorphonuclear cells travelling from peripheral blood to the ulcer, is thought to inhibit pathogen colonization (Peral et al. 2010).

8 Future Perspectives

The new insight and healing potential of advantageous microbial probiotics are illustrated in the book chapter as an alternative and healthy approach to treating patients with skin-related wounds/disorders. The examination of microbiota, including beneficial microorganisms by using high-throughput genomic technologies, will elucidate new pathways and molecular mechanisms that can improve our knowledge of how commensal microbes, including non-healing wounds, can cope with different diseases. Moreover, it is important to identify cross-communication among the beneficial microorganisms and the host's respective pathways. The selection of bacterial species is of particular significance, because the impacts of probiotic bacteria can be highly strain-specific. Their incorporation as an integrative therapy provides new possibilities to treat patients with wound healing disorders, taking into account the studies expended on probiotics and their important role in human health.

9 Conclusions

Based on recent in vitro and in vivo research, this book chapter documents the ability of cellular components or probiotic metabolites to promote skin health and dermatological advancement. Although numerous investigations have indicated encouraging potentials of probiotics and their supernatants for skin health, we predict that such an argument for skin health is still at its early stages, with the requirement of more comprehensive final topical applications and human trials (well-designed) to validate the exact doses required, safety and regulatory compliances, possible side effects, host dependency, and, essentially, the precise mechanisms for indirect and direct actions of the live cells and/or therapeutic compounds. The microbial colonization occurs immediately after injury, and the cross-talk between the innate immune response, pathogens and microflora almost simultaneously begins. Cutaneous microbiota has an advantageous impact on the wound curing process through several potential processes, both positively and harmfully, dependent on the microorganisms prevailing in the area of the wound. The identification of microorganisms derived from the nonspecific immune (innate) response is essential for triggering the process of wound healing, and particularly for the preliminary stage of severe (acute) inflammation. The microbe *S. aureus*, however, can cause infection, impaired healing of chronic and acute wounds. Besides the microflora on skin, the gastrointestinal microorganisms may similarly influence the wound curing process, by influencing, indirectly or directly, several features that control the therapeutic potential, e.g. blood pressure, tissue oxygenation levels, immune response and inflammations. Furthermore, several mechanisms have been recognized as to how the gut microbiome could affect the energy metabolism of the host and thus the incidence of indications of metabolic syndrome, e.g. Diabetes, hypertension, obesity and hyperlipidemia, which were also associated with very slow wound healing. For a substantial portion of the population, impaired wound healing is a major reason for morbidity and mortality. Taking the above seriously, the scientific community guides the investigation to a deeper understanding of the cross-talk amongst host immune response and microorganisms, with the objective of developing new methods for therapeutic wound care based on the therapeutic use of probiotic microbes. The probiotics are advantageous host microbes and, on the basis of evidence so far, may have a positive effect on the wound curing process. Probiotics administration has been associated with improvements in the topical and per os wound curing process. Is the management of the human microbiome, gastrointestinal as well as cutaneous, essentially crucial for the chronic wounds and ulcers treatment therapies that have eluded us so far, or is it just another factor that needs to be taken seriously for this therapeutic entity to be treated? Time is going to say.

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