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Protecting the outside: Biological tools to manipulate the skin microbiota

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Abstract

Interest surrounding the role that skin microbes play in various aspects of human health has recently experienced a timely surge, particularly among researchers, clinicians, and consumer-focused industries. The world is now approaching a post-antibiotic era where conventional antibacterial therapeutics have shown a loss in effectiveness due to overuse, leading to the looming antibiotic resistance crisis. The increasing threat posed by antibiotic resistance is compounded by an inadequate discovery rate of new antibiotics and has, in turn,

resulted in global interest for alternative solutions. Recent studies have demonstrated that imbalances in skin microbiota are associated with assorted skin diseases and infections. Specifically, restoration of this ecosystem imbalance results in an alleviation of symptoms, achieved simply by applying bacteria normally found in abundance on healthy skin to the skin of those deficient in beneficial bacteria. The aim of this review is to discuss the currently available literature on biological tools that have the potential to manipulate the skin microbiota, with particular focus on bacteriocins, phage therapy, antibiotics, probiotics, and targets of the gut-skin axis. This review will also address how the skin microbiota protects humans from invading pathogens in the external environment while discussing novel strategies to manipulate the skin microbiota to avoid and/or treat various disease states.

Keywords: skin microbiota, bacteriocin, phage, probiotics, gut-skin axis

Introduction

The first line of defence against the outside world for humans is their skin, the largest organ of the body comprising 12-15% of total body weight with a surface area of $2m^2$. However, much like the human small intestine possessing villi that increase available surface area, the skin also includes discrepant features that make such calculations difficult. Furthermore, studies also show that the skin microbiota extends into the dermis, challenging the notion that deeper layers of the skin are protected from bacteria (Lange-Asschenfeldt *et al.* 2011; Nakatsuji *et al.* 2013). It has therefore been proposed that the average surface area of microbiota-colonised human skin be increased from $2m^2$ to $30m^2$, to include approximately 5 million appendages (such as sweat ducts and hair follicles).

The skin is composed of two layers: the *epidermis* and the *dermis*. The epidermis is the skin's top stratum and is subdivided into three layers, namely the *cornified*, *granular* and

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Malpighian layers. The cornified layer is the body's first barrier to the external environment, predominantly composed of dead cells. Keratinocytes are located in the granular layer, while melanocytes reside in the Malpighian layer. Below the epidermis is the dermis layer, rich in collagen and elastin, giving skin strength and elasticity. The dermis layer is comprised of sebaceous glands, hair follicles, nerves, capillaries and blood vessels (Yousef and Sharma 2018).

Unlike the 'jungle' of the gastrointestinal (GI) tract, the ecology of skin is predominantly akin to a desert-dry, vast and lacking nutrients. While the exact composition of the skin microbiota in healthy individuals is still unknown, we imagine, similar to the gut, that the microbial composition is quite individualistic and is dependent on many factors such as sex, hygiene, delivery mode, cohabitation, and geography (Cuscó *et al.*, 2017; Lunjani *et al.*, 2019). The skin exhibits widely varying pH and temperature profiles across its surface, and, while some regions are relatively densely populated, only certain bacterial phyla colonise: Proteobacteria, Firmicutes, Bacteroidetes and Actinobacteria, with the latter being the most diverse and prevalent phylum in healthy skin (Gao *et al.* 2008). Key human skin bacterial residents include *Staphylococcus*, *Corynebacterium, Cutibacterium* (formally known as "*Propionibacterium*", (Scholz and Kilian 2016)), *Micrococcus*, *Streptococcus*, *Brevibacterium, Acinetobacter,* and *Pseudomonas* (Rosenthal *et al.* 2011). Microbial composition is dependent on optimum growth conditions and phenotypic preferences, different microbes reside in various areas of the skin. For example, *Cutibacterium* species dominate lipophilic areas such as the back, while *Staphylococcus* and *Corynebacterium* appear to be the dominant populations in moist areas such as the inguinal crease or toe webspace area, and Gram-negative microbes populate dry areas like the volar forearm (Grice *et al.* 2009; Grice and Segre 2011; Byrd, Belkaid and Segre 2018).

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While in recent years it was suggested that an overabundance of certain bacterial genera was the root cause of particular skin disorders (for example, a surge in *Cutibacterium acnes* (*C. acnes*) results in the development of acne vulgaris), it is now generally recognised that the disequilibrium between larger microbial communities might be one additional and important factor behind the pathogenesis of selected skin diseases (Fitz-Gibbon *et al.* 2014). Furthermore, evidence of the link between gut and skin microbiomes is growing, with many studies demonstrating how the GI ecosystem acts as a major regulator of the gut-skin axis (Arck *et al.* 2010; O'Neill *et al.* 2016; Vaughn, Notay and Clark 2017; Salem *et al.* 2018).

The looming threat of antibiotic resistance has increased awareness to the need for alternative antimicrobial therapies, thus it is imperative to have a clear understanding of the mechanisms of action. This review presents current and novel treatment strategies for various skin diseases, to generate a greater comprehension of how different therapeutic interventions can manipulate the skin microbiota.

Microbiota imbalances associated with skin diseases and an overview of current, existing and conventional treatments

Here we review what is known of the role of microbes in the pathogenesis of skin diseases and some of the therapies either currently in use or under development to ameliorate some of these skin pathologies, see table 1.

Impetigo

Impetigo is a common skin infection particularly in children, linked to a surge of either *Staphylococcus* and/or *Streptococcus* species. Similar to atopic dermatitis, the most common

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cause is an overabundance of *Staphylococcus aureus* which produces toxins, such as exfoliative toxins A and B, that disrupt epidermal cells, resulting in blister formation. There are 2 types of impetigo: bullous (blister-shiny lesions) and non-bullous (crusted lesions), the latter being most common (70% of impetigo cases), (Pereira 2014). Current treatments include both systemic and topical antibiotics, the latter is more favourable where fusidic acid and Mupirocin are commonly used. Systemic treatments include a variety of macrolide antibiotics such as erythromycin (Hartman-Adams, Banvard and Juckett 2014). A new topical biological treatment for impetigo is Ozenoxacin, a novel quinolone antibiotic that targets *S. aureus* and *Staphylococcus pyogenes*. Ozenoxacin inhibits DNA replication by targeting DNA gyrase A and topoisomerase IV (Sahu and Mishra 2018).

Atopic dermatitis (AD)

AD is an inflammatory skin condition characterised by red, itchy and eczematous lesions (dry skin patches). It can be both chronic and recurrent and affects children primarily. AD pathogenesis is associated to an imbalance of coagulase negative staphylococci that results in a surge of *S. aureus* as well as a reduction in other skin commensals such as *Streptococcus, Cutibacterium, Prevotella, Acinetobacter, Corynebacterium* species (Dekio *et al.* 2007; Kong *et al.* 2012; Bjerre *et al.* 2017; Sun *et al.* 2019).

There are numerous treatments used currently to treat AD and these include topical corticosteroids (main treatment), antiseptic treatments: octenidine and chlorhexidine, and topical antibiotics: mupirocin, fusidic acid and retapamulin (Nowicki *et al.* 2015). The effect of a topical lotion was demonstrated by Blanchet-Réthoré *et al.*, (2017). By topically applying a lotion containing a heat-treated strain of *Lactobacillus johnsonii* (NCC 533) to the skin of AD patients, the abundance of *S. aureus* decreased after 3 weeks. The probiotic strain

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was heat-treated to ensure that the beneficial *Lb. johnsonii* did not replicate. Other novel treatments are discussed later in this review.

Acne vulgaris

Cutibacterium acnes is an anaerobic skin commensal associated with the pathogenesis of the skin disease acne vulgaris more commonly known as acne (Liu *et al.*, 2015). Contrary to previous reports that increased abundance of *C. acnes* was the driving force behind acne vulgaris, it is now recognised that *C. acnes* is the most dominant bacterial species within the pilosebaceous follicle for both acne and non-acne sufferers. Bek-Thomsen et al., (2008) compared the microbial diversity of follicles of acne patients to healthy individuals using 16S rRNA genes (n=8). *C. acnes* was discovered in the follicles of both groups while *S. epidermidis* and low amounts of other species were also present in acne patients. It is now thought that a loss of diversity of skin microbiota coupled with initiation of innate immunity is linked to the pathogenesis of this inflammatory condition (Barnard *et al.* 2016; Szabó *et al.* 2017; Dréno *et al.* 2018).

Certain *C. acnes* strains namely type1A, are linked to both the progression of acne and the increased severity of lesions and scars in acne patients (Fitz-Gibbon *et al.*, 2014; Pécastaings *et al.*, 2018). Current treatments of acne vulgaris have been extensively reviewed by Rathi, 2011; in brief, they include topical benzoyl peroxide or salicylic acid, topical antibiotics: clindamycin, or oral antibiotics: erythromycin and tetracyclines, topical retinoids (vitamin A derivatives) and oral retinoids: isotretinoin (more commonly known as Roaccutane). *Myrtus communis* is a species of myrtle plant common to the Mediterranean region; from its leaves an isopropyl acetate extract Myrtacine® is prepared. Feuillolay *et al.*, 2016 demonstrated that alone or in combination with erythromycin, Myrtacine® can penetrate the biofilm formed by

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C. acnes in antibiotic resistant states. Antibiotic potency improved when in combination with Myrtacine®. Pécastaings *et al.*, 2018 showed *in vivo* that a Myrtacine® based cream lowered the levels of erythromycin resistant *C. acnes* and was further linked to a decrease in acne lesions.

Psoriasis

Psoriasis is a skin inflammatory autoimmune disease, characterised by dry, red, itchy, scaling patches on the skin, predominantly evident on the face and trunk of the body. Skin microbiota namely *Corynebacterium*, *Cutibacterium*, *Staphylococcus,* and *Streptococcus* species may contribute to the pathogenesis of chronic plaque psoriasis. Gao et al., (2008) reported a 'substantial alteration' in skin microbial composition (n=6) from swabs, when using 16S rRNA genes to assess the skin microbiota in healthy and psoriatic skin. Firmicutes were observed at higher levels, while *Actinobacteria* and *Cutibacterium* exhibited decreased abundance in psoriatic skin when compared to healthy persons, Alekseyenko *et al.*, (2013) reported similar results. However, Fahlen *et al.*, (2012) employed skin biopsies (n=22) and found no difference in levels of Firmicutes or Actinobacteria between healthy and psoriatic skin, but observed significantly higher levels of Proteobacteria in psoriatic skin on the trunks of patients when compared to healthy subjects. The role skin microbiota play in the pathogenesis of psoriasis remains unclear (Benhadou *et al.* 2018). Current treatments include topical corticosteroids (most frequently prescribed), anthralin, derived from goa powder from the araroba tree (which functions in slowing growth of skin cells), vitamin D analogues, topical retinoids, and coal-tar among others. Novel treatments are immunotherapy focused; for example interleukin antagonists and inhibitors, adenosine receptor agonists, tumour necrosis factor antagonists, janus kinase and phosphodiesterase inhibitors (Mahil, Capon and Barker 2016).

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Rosacea

Rosacea is an inflammatory skin disease that is characterised by redness, flushing, pimples, pustules, dilated blood vessels and thickening of the skin (Mikkelsen *et al.* 2016). It is linked to immune dysfunction and neurovascular dysregulation. There are 4 major subtypes of rosacea erythematotelangiectatic, papulopustular, phymatous, and ocular. Current treatments target inflammatory pathways involved in the pathogenesis of rosacea and are predominately topical including metronidazole, azelaic acid, ivermectin, and brimonidine tartrate, oxymetazoline hydrochloride with doxycycline the only approved oral drug (Rainer, Kang and Chien 2017; Engin *et al.* 2020)**.** Recently a study by Rainer *et al.*, (2020) (n=38: 19 healthy, 19 rosacea) showed that the skin microbiota of individuals with rosacea appear to have greater abundance of *Corynebacterium kroppenstedtii, Campylobacter ureolyticus* and *Prevotella intermedia* and decreased levels of *Roseomonas mucosa* when compared to healthy subjects.

Cutaneous leishmaniasis

A vector borne tropical parasitic disease called cutaneous leishmaniasis (CL) is a growing problem especially in developing countries, with 12 million cases globally and 1.5 million new cases diagnosed every year. CL is transmitted by the female sand-fly and presents on the skin as an erythematous papule that develops into an ulcer with a raised and distinct border (Markle and Makhoul 2004). In mice this disease induces dysbiosis within the skin microbiota (a surge in abundance of *Staphylococcus* and *Streptococcus* species) resulting in inflammation (Gimblet *et al.* 2017). Amphotericin B, an antibiotic originally isolated from *Streptomyces nodosus,* is a powerful antifungal agent and was found to have a positive effect

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at eliminating these ulcers (Mushtaq, Dogra and Dogra 2016). No studies investigating the restoration of skin microbiota has been documented as of yet, however, as skin appears normal after treatment and due to general mode of action of amphotericin B binding to ergosterol damaging cell membrane integrity, one can speculate that the healthy microbiota is also restored.

Skin cancer

Information regarding the microbiota of skin melanoma is scarce however a recent study by Mrázek *et al.*, (2019) found that the microbial diversity of healthy and melanoma pig skin tissue were significantly different, whereby melanoma samples showed increased levels of *Fusobacterium* and *Trueperella* genera. Further characterisation is required to explore the link of these microbial differences with melanoma and skin cancer and to detect if a skin microbe could be employed as a biomarker for melanoma.

Fungal skin infections

Fungi appear to play a functional role in the skin microbiome, albeit that their exact role is not fully understood (Findley *et al.* 2013). *Malassezia* is the most abundant genus of fungi present on human skin and is present across different body sites. *Malassezia* is an opportunistic pathogen and is linked both directly and indirectly via immune system to many skin conditions including dandruff, atopic eczema/dermatitis, pityriasis versicolor, seborrheic dermatitis, and folliculitis (Underhill and Iliev 2014; Limon, Skalski and Underhill 2017). It can induce skin inflammation through the production of fatty acids (Harada *et al.* 2015).

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Current broad spectrum anti-fungal treatments for numerous fungal skin infections such as 'dermatophytosis of the foot' (athletes foot), candida and ringworm include clotrimazole, miconazole, econazole, ketoconazole, naftifine, terbinafine, and Amphotericin B (Bell 2007; Hay 2018).

Some non-antibiotic methods to influence the skin mycobiota include zinc pyrithione (ZPT), synthesised from the antimicrobial metabolite aspergillic acid, that displays a broad spectrum of activity inhibiting fungi, Gram-positive and -negative bacteria (Schwartz 2016). The exact mode of action of ZPT is not fully understood but it is thought to inhibit mitochondrial function, amplify levels of cellular zinc and reduce expression of lipases. ZPT is commonly used in anti-dandruff shampoos (Saunders, Scheynius and Heitman 2012; Park *et al.* 2018). Liposomes, niosomes, ethosomes, microemulsions, nanoparticles, microspheres and micelles have all been proposed as novel delivery agents for anti-fungal skin treatments. Use of such novel interventions results in enhanced bioavailability, reduced side effects, and deeper diffusion of anti-fungal drugs into the skin (Kumar et al., 2014). In a clinical trial of duration 56 days involving 60 males with moderate to severe dandruff, Reygagne et al., (2017) found that intake of the oral probiotic *Lactobacillus paracasei* NCC2461 ST11 significantly lessened the severity of dandruff, potentially by influencing the skin barrier and immune system. This study again highlights the gut-skin connection, whereby treating the gut results in benefit to the skin microbiome. The precise role mycobiota play in modulating skin disorders remains to be fully comprehended.

The Gut–skin-brain connection

The hypothesis of a gut-skin-brain connection was first put forward in the 1930s by Stokes and Pillsbury when it was theorised that a physiological overlap between the three regions

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existed, see figure 2. These early researchers postulated that brain emotions such as stress and depression impact the gut, altering the overall microbial composition which in turn increases the permeability of the intestines and thereby leads to the pathogenesis of skin diseases like 'erythema, urticaria and dermatitis' (Stokes and Pillsbury 1930). In 1981 another link of the gut-skin-brain axis was reported whereby 'peptide-containing cells in skin, brain and gut' arise from a common embryonic origin- dopaminergic precursors (Teitelman, Joh and Reis 1981). Arck *et al.*, (2010) reviews the existence of a gut-brain-skin axis and presents the gut as the origin of many skin diseases, see figure 2. Arck *et al*., also report that the ingestion of probiotics in mice beneficially affected the skin microbiota by reducing skin inflammation, restoring homeostasis, improving hair growth and stress responses in tissues,

Additionally, the brain-gut and gut-brain connections are also well established and more recently it has become widely accepted that the interactions are bi-directional. For example, Parkinson's disease (PD) was originally described as a 'shaking palsy' in 1817 and thought to be a disease that began in the brain and spread throughout the body. However, it was also noted at that time that by treating GI complaints such as constipation, the motor function of patients improved. Now ground-breaking research using animal models is demonstrating that injections of alpha-synuclein (prion involved in the pathogenesis of PD) into the gut induces PD related brain pathology and symptoms, indicating that the gut-brain connection is indeed bi-directional (Martin *et al.* 2018; Uemura *et al.* 2018; O'Donovan *et al.* 2019). This supports the hypothesis that the skin-gut connection may be also bi-directional and that many skin diseases also may begin in the gut.

Hill *et al.*, 2017 reported that the mode of delivery of infants can shape the composition of their gut microbiota. In comparison to babies born via the birth canal (whose gut microbiota remains relatively stable over the first six months), the initial microbiota of babies born via caesarean section is less established, with more Firmicutes and less Actinobacteria present in

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their faecal material. Differences between natural and caesarean delivery can still be observed at 24 weeks, however, variances diminish over time. Specifically, the microbial composition of the babies' gut depends on which microbes first colonise the skin (Rodríguez *et al.* 2015). This suggests the presence of a skin- gut axis and opens the door for many mechanistic questions: Can coating our skin with topical probiotics have an impact on the microbial composition of the gut? Does the brain transmit signals to the gut which in turn communicates to the skin, or are these signals initiated in the gut?

The skin and brain are connected through the hypothalamic-pituitary-adrenal (HPA) axis which links stress effects to the skin (Arck *et al.* 2006; Chen and Lyga 2014). Both psychological and environmental stress stimulate secretion of stress hormones along the HPA axis, such as corticotropin-releasing hormone (CRH). Binding of CRH to its receptor initiates a cascade of events, one such example being the secretion of adrenocorticotropic hormone (ACTH) which in turn stimulates the release of glucocorticoids such as cortisol, (the primary stress hormone), from the adrenal cortex. Interestingly, both CRH and ACTH are produced in skin cells thereby establishing the skins own peripheral HPA axis (Kim *et al.* 2013). Prolactin (PRL) is released from the brain which in turn stimulates sebum production and keratinocyte proliferation. In the skin, prolactin is thought to modulate epithelial cell growth through a number of pathways including altering cytokine release in the skin and through prolactin's ability to bind specific skin receptors (Paus 1991). Calcitonin gene-related peptide and substance P are upregulated in the dorsal root ganglia, thus inducing an immune response triggering production of inflammatory cytokines and activation of mast cells, resulting in neurogenic inflammation in the skin. There is now a strong brain-skin connection that can negatively affect skin functions and disease.

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Small intestinal barrier overgrowth (SIBO)

SIBO is defined as 'an increase in the relative abundance and/or alteration in the type of bacteria in the upper gastrointestinal tract' (Bures *et al.* 2010). Interest surrounding intestinal permeability is growing, as scientists continue to uncover links to several human diseases such as autoimmune disease (Visser *et al.* 2009), liver disease (Cariello *et al.* 2010) and acne vulgaris (Bowe and Logan 2011) to name a few. This paragraph focuses on how intestinal permeability manifests itself in skin diseases and how such maladies can be alleviated. It was hypothesised by Stokes and Pillsbury in 1930, and has since been reported by Salem *et al.*, 2018, that hypochlorhydria (low production of stomach acid) leads to the presence of colonic bacteria in the small intestine, resulting in inflammation and dysbiosis i.e. SIBO. O'Neill *et al.*, 2016 eloquently illustrated mechanisms for different pathways potentially involved in the gut-skin axis in relation to SIBO and proposed how metabolites (either generated from microbial metabolism or consumed from one's diet) reach the skin and result in pathological changes. The same researchers also reviewed current literature to determine how allergies to foods like peanuts are more likely to occur when the skin is exposed to peanuts before the gut, while also discussing the degree to which high-fat western diets can lead to overstimulation of lipid production in sebaceous glands of hair follicles via the mTor-FoxO1 pathway.

Colonic bacteria are associated with the production of short-chain fatty acids (SCFAs) such as propionic acid and butyric acid. In the colon, colonocytes are present which absorb 95% of SCFAs (Gougerot and Peyre 1936; Wong *et al.* 2006). However, colonic bacteria can also be found in the small intestine (Salem *et al.* 2018) and we hypothesise that this may contribute to its inflammation. It is well documented that the enteric nervous system (ENS) is

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responsible for motor function of the large intestine, however only recently has the pattern of neuronal activity of the ENS, that generates contractions in the smooth muscle of the GI, been identified (Spencer *et al.* 2018). This study demonstrated that the gut could produce its own neuronal pattern and can function independently to the brain, like a "second brain." Is the gut our communication station or the central processing unit of our bodies? Further investigations into the gut's mechanisms of communication with the skin and other organs of the body are clearly warranted. While much work is required to identify such mechanisms of communication and determine how experimental outcomes can be manipulated to alleviate actual human disease symptoms, it remains clear that there is immense potential for further research into the gut-skin axis. Stokes and Pillsbury were indeed well ahead of their time.

Biological tools to treat skin diseases- direct

Table 2 summarises the following biological tools that are used or have potential to modulate the skin microbiota as is also depicted in figure 1.

Antimicrobial peptides (AMPs)

AMPs are small polypeptide molecules (<10kDa), produced by our skin cells and skin microbiota and are part of the innate immune system. As their name suggests, AMPs are antimicrobial by nature but also function by modulating immune responses. The amphipathic nature and positive charge of AMPs aids in their role in disrupting the negatively charged phospholipid membrane of target cells (Hancock and Sahl 2006). Takahashi and Gallo, 2017 recently reported that there are at least 20 AMPs produced by our skin and skin bacteria; with keratinocytes as the main producers and cathelicidins and defensins being the two major groups of skin AMPs (Bardan, Nizet and Gallo 2004; Smet and Contreras 2005). Impairment

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of the epidermal layer of skin is a common result of skin disorders. AMP production is downregulated in skin diseases like atopic dermatitis (AD) resulting in a surge in *S. aureus* but upregulated in psoriasis and rosacea where it results in inflammation (Pfalzgraff, Brandenburg and Weindl 2018), this could be a plausible reason as to why AD sufferers are more susceptible to skin infection than patients with psoriasis (Marcinkiewicz and Majewski 2016). Defensins display a broad range inhibition spectrum being antimicrobial, antifungal and antiviral by nature.

Defensins and cathelicidins both have an overall net positive charge enabling them to bind to the negatively charged membranes of bacteria and permeabilise the cells. They work synergistically: defensins modulate receptors on immunocompetent cells inhibiting viruses from binding and infecting such cells while cathelicidins are expressed in response to inflammatory stimulus. For example, cathelcidin LL-37 signals the migration of mast cells, neutrophils, monocytes and T cells to sites of inflammation, modulates immune responses and is involved in wound healing (Korting *et al.* 2012). While many reviews describe the mechanisms of action of various AMPs and studies of novel AMPs as potential therapeutics in skin diseases, few have made it past clinical trials or reached the marketplace due to production cost, efficacy and their potential cytotoxicity (Steinstraesser *et al.* 2008; Brogden and Brogden 2011; Kang *et al.* 2017). For example, omiganan, a cationic AMP, is being investigated as a novel therapeutic in the treatment of acne and rosacea and has passed stage III of clinical trials, while pexiganan a novel treatment of foot ulcers in patients with diabetes mellitus also entered phase III clinical trials but was not FDA approved (Korting *et al.* 2012).

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Bacteriocins

Bacteriocins, a type of AMP, are small, ribosomally synthesised peptides that are heat stable, produced by bacteria to kill their competitors (Cotter, Ross and Hill 2012). Interest surrounding the therapeutic potential of bacteriocins is increasing (Behrens *et al.* 2017). Bacteriocins have an associated probiotic potential: they help bacterial colonisers become established in a particular environment; they can inhibit competitors or pathogens, alter the skin microbiota and communicate with the immune system (Dobson *et al.* 2012). Gillor, Etzion and Riley, (2008) suggested that bacteriocins have both anti- and probiotic properties. The first bacteriocin discovered was colicin by Gratia in 1925, when he observed that *E. coli* strains slowed/inhibited the growth of surrounding bacteria. Soon after in 1928, Rogers found that some *Lactococcus lactis* strains had inhibitory ability against *Lactobacillus bulgaricus*; this antimicrobial Nisin has since become the most characterised and well-known bacteriocin. Nisin is a food preservative that was approved by the FDA in 1988 and since has many applications (van Kraaij *et al.* 1999; Cheigh and Pyun 2005; Shin *et al.* 2016). The main mode of action of bacteriocins is to disrupt the cell membrane of the target organism to cause cell death. For example, the N- terminus region of Nisin attaches to target cell membrane and forms a complex with lipid II, a fundamental component in cell wall synthesis, that disrupts the membrane allowing the C-terminus end of nisin to enter the target cell causing cell permeabilisation and death (Healy *et al.* 2013). Bacteriocins are divided into 3 classes, which are further subdivided into groups based on their structures (Cotter, Hill and Ross 2005; van der Donk and Nair 2014; Yang *et al.* 2014). Class II bacteriocins are a broad group that unlike class I, do not undergo posttranslational changes, while class III consists of bacteriolysins which are large proteins that function in lysing target bacteria by inducing cell wall hydrolysis (Cotter, Hill and Ross 2005; Sang and Blecha 2008). Given their potential for further development into future antimicrobial therapies, we will concentrate on class I

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bacteriocins. For this review we will focus predominantly on bacteriocins produced by skin bacteria that can target skin pathogens and discuss bacteriocin based therapies for skin ailments.

Lantibiotics

Lantibiotics are Class I bacteriocins which consist of post-translationally modified peptides that contain some unusual amino acids namely 2,3-didehydroalanine (Dha) and 2,3-dehydrobutyrine (Dhb) – dehydrated derivatives of serine and threonine, respectively. Class I bacteriocins also contain the lanthionine residues, Lan and MeLan formed as a result of a reaction between cysteine with either Dha or Dhb, respectively. This results in the formation of Lan or MeLan bridges and gives lantibiotics their polycyclic structure (McAuliffe, Ross and Hill 2001). Lantibiotics (lantithione-containing antibiotic) are subdivided into 2 groups type A and B. Type A are cationic peptides of length ~34 amino acids and function by disrupting membrane integrity, while type B are globular shaped consisting of ~19 amino acids and function by inhibiting cell wall biosynthesis. Nisin, a lantibiotic, is a class Ia bacteriocin and as a result of its success, lantibiotics are of particular interest. A number of lantibiotics have been isolated from staphylococcal human commensals including epidermin, hominicin and gallidermin, that exhibit inhibitory activity on bacteria associated with skin dysbiosis (Götz *et al.* 2014).

Originally isolated from chickens and pheasants, gallidermin is produced by *S. gallinarum*, and, while the bacterium is widespread in nature it is also present in healthy human saliva (Shi *et al.* 2015). Kellner *et al.*, (1988) demonstrated the inhibitory activity of *S. gallinarum* (F16/ P57) Tu3928, against *Cutibacterium* species, key players in the pathogenesis of acne. Epidermin produced by *S. epidermidis*, was the first staphylococcal lantibiotic discovered to

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undergo post-translational modifications (Götz *et al.* 2014). Gallidermin and epidermin have displayed inhibitory activity against *C. acnes* as well as a number of *Staphylococcus* and *Streptococcus* species (Kellner *et al.* 1988; Bonelli *et al.* 2006), and while *S. gallinarum* and *S. epidermidis* are recognised skin commensals they can also be cutaneous pathogens (Shields, Tschetter and Wanat 2016). Coagulase-negative staphylococci (CoNS) are regarded as normal skin commensals, however more and more studies are highlighting them as the root cause of skin and soft tissue infections, due to their 'opportunistic pathogenic' nature, (Davis *et al.* 2013).

The probiotic potential of *S. hominis* (women's vaginal isolates MBBL 2-9) against *S. aureus* was reported by Sung *et al.*, 2010. They described the *S. hominis* strain as tolerant to acid, resistant to bile and capable of adhering to an epithelial cell line; all of which are considered important probiotic properties. They found the strain also produced a bacteriocin. Further characterisation of this bacteriocin was carried out by Kim *et al.*, 2010, where they described a novel antimicrobial peptide named 'hominicin'. Hominicin displayed inhibition against *S. aureus*, Methicillin-Resistant *Staphylococcus aureus* (MRSA) and VISA (vancomycin-intermediate *S. aureus*), and contained uncommon amino acids, similar to those found in Class I bacteriocins.

Nukacin ISK-1 is a bacteriocin produced by *S. warneri*, originally isolated from a nukadoko (a fermented rice bran bed, used for the nukazuke method of pickling vegetables) (Kimura *et al.* 1997). Nukacin ISK-1 was further characterised as a broad spectrum type (II-A) lantibiotic with the ability of inhibiting some *Staphylococcus* species (Sashihara *et al.* 2000). Janek *et al.*, 2016 discovered a *S. epidermidis* strain that produced a nukacin like variant (normally produced by *S. warneri*), residing on a plasmid within the *S. epidermidis* genome and also noted that a *S. hominis* strain (KQU-131), isolated from Thai fermented marine fish by Wilaipun *et al.*, 2008, produced another nukacin variant and suggested that

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Staphylococcus strains exchange diverse bacteriocin genes on a frequent basis. Nukacin ISK-1 is a broad spectrum lantibiotic with reported inhibitory capabilities against *Bacillus, Listeria, Lactococcus, Micrococcus, Lactobacillus* and *Enterococcus* species (Asaduzzaman *et al.* 2009).

L. salivarius is a well-documented and characterised probiotic strain (Ocaña, Pesce de Ruiz Holgado and Nader-Macías 1999; Stern *et al.* 2006; O'Shea *et al.* 2011; Messaoudi *et al.* 2013), with both *in vitro* and *in vivo* studies demonstrating the bacteriocin capabilities of certain *L. salivarius* strains. Deidda *et al.*, 2018 reported that *Lactobacillus salivarius* LS03, a probiotic strain, exhibited specific antimicrobial activity and anti-inflammatory activity targeted at Il-8. They demonstrated, via the disc diffusion method, that *L. salivarius* LS03 inhibited growth of *C. acnes*. While Corr *et al.*, 2007 showed that the bacteriocin produced by *L. salivarius* UCC118 (Abp118) prevented harm to mice infected with *Listeria monocytogenes* (serious food borne pathogen) by comparing it to a mutant of the same strain unable to produce Abp118.

Other bacteriocins

Cebrián *et al.*, (2018) found that bacteriocin AS-48, produced by *Enterococcus* species, displayed inhibitory activity against *C. acnes.* Improvement in inhibition was noted when this bacteriocin was combined with lysozyme, a natural antimicrobial found throughout the animal kingdom in bodily fluids, including tears, saliva, sweat and blood (Ragland and Criss 2017). Cebrián *et al.*, (2018) further demonstrated that a combination of bacteriocin AS-48 and lysozyme was not cytotoxic suggesting it might be a good alternative antimicrobial therapy for acne vulgaris.

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Oh *et al.*, 2006 demonstrated *Lactococcus* sp. HY 449 produces a bacteriocin that displayed inhibitory effects on bacteria involved in skin inflammation including *Staphylococcus epidermidis, S. aureus, C. acnes* and *Streptococcus pyogenes*. A human patch test carried out on healthy female volunteers, (n=30), confirmed this bacteriocin did not irritate the patients' skin, rendering it a suitable antimicrobial for addition to cosmetic products.

Nakatsuji *et al.*, 2017 demonstrated that development of a personalised probiotic cream could alleviate the symptoms of Atopic Dermatitis (AD) more commonly referred to as eczema. In AD, imbalances in the skin microbiota occur; there are deficiencies of certain skin bacteria such as CoNS and increases in other bacteria, such as a surge in *S. aureus*. They reported that human commensal *Staphylococcus* species produce AMPs which naturally protect against the skin pathogen *S. aureus*, a key player in atopic dermatitis (AD). In this study antimicrobial producing CoNS, that were abundant on healthy individuals and not on AD patients, namely *S. epidermidis* and *S. hominis*, were added to a skin cream 'Cetaphil lotion' and introduced onto the skin of 5 AD patients in an *in vivo* study. Application of the 'antimicrobial lotion' to the affected body area resulted in a significant decrease in the numbers of *S. aureus* when compared to control subjects. They demonstrated that the inhibitory activity of the *S. hominis* strains applied was specific to *S. aureus*, including an MRSA strain, and did not inhibit other bacteria commonly present on human skin namely *S. epidermidis, C. acnes, and Corynebacterium minutissimum*. This study shows imbalances within the skin microbiota can lead to pathogenesis of skin diseases and demonstrates that skin commensal bacteria can alleviate the symptoms and restoring this imbalance.

A recent study by our group, O'Sullivan *et al.*, (2019), demonstrates the antimicrobial power of staphylococci isolated from different areas of human skin on human pathogens. Certain CoNS produced putative novel bacteriocins that exhibited inhibitory effects against potential skin pathogens such as MRSA, *C. acnes, S. epidermidis*.

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Phenol soluble modulins (PSM)

PSM, another type of AMP, is a group of peptides produced by microbiota that have several roles in pathogenesis including blood cell lysis and inflammation. PSMs also aid in the growth and spread of staphylococci on the skin, as well as contributing to their virulence (Cheung *et al.* 2014). Despite their virulence, antimicrobial ability of some PSMs has been reported. Cogen *et al.*, 2010 and Cogen, Yamasaki, Muto, *et al.*, 2010 observed that PSMs namely, PSMγ and PSMδ produced by human skin commensal *S. epidermidis* exhibited similar properties to AMPs; functioning in cell membrane disruption resulting in cell death. PSMγ and PSMδ inhibited skin pathogen *S. aureus* and also protected against group A streptococci. Given that the PSMs can inhibit other microbes without inhibiting the producing organism, it could be that PSMs give *S. epidermidis* a competitive advantage demonstrating the beneficial association of a skin commensal with skin epithelia.

Short-chain fatty acids (SCFA)

The association of increased abundance of *C. acnes* and *C. granulosum* with healthy skin has led to the proposition of their probiotic potential (Barnard *et al.* 2016). Fermentation of carbohydrates by bacteria results in the production of SCFAs (den Besten *et al.* 2013). SCFA impacts skin pH by increasing acidity thus protecting against pathogens. While *C. acnes* is a skin pathogen that has been associated with a number of skin conditions, it can also have beneficial effects. For example, Shu *et al.*, 2013 demonstrated the antimicrobial potential of *C. acnes* in its ability to inhibit the growth of a dominant MRSA strain (USA300), both *in vitro* and *in vivo* in a mouse skin model by fermenting glycerol, (a carbon source that is also a natural skin metabolite (Fluhr, Darlenski and Surber 2008)), by *C. acnes*. Similarly Wang *et*

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al., 2014 demonstrated fermentation of glycerol by skin commensals- predominantly *S. epidermidis*, resulted in the production of succinic acid which suppressed the growth of *C. acnes* on a mouse skin model.

Phage therapy

Phage therapy is another alternative therapy to antibiotics and a number of research centres now focus on the development and delivery of phage therapy (www.phagetherapycenter.com; www.iitd.pan.wroc.pl/en/OTF/). While bacteria can also become resistant to phage, it is comparably easier to isolate a new phage than develop a new antibiotic. Though a comprehensive understanding of the effect of phage therapy on the skin microbiota remains to be derived (Schommer and Gallo 2013), there is currently an increasing interest surrounding phage treatment as a therapeutic option.

Phage: mode of action

A bacteriophage (phage) is a virus that infects bacteria. Phages can replicate via the lytic or lysogenic cycle; both types of phage attach to the host bacterial cell and injects its DNA into the cell. During lytic infection, the phage hijacks the host machinery for its own replication and assembly of phage particles which is followed by cell lysis and release of progeny phages. During the lysogenic cycle, phage DNA integrates into the host DNA and thus replicates in accordance with the host and is referred to as a prophage. When conditions are suitable the cycle switches to the lytic cycle (Sulakvelidze, Alavidze and Morris Jr 2001). Phage therapy generally exploits exclusively lytic phage. Hence phage, normally with a narrow host range, can reduce the number of bacteria in the environment and so can impact on both the structure and function of bacterial communities in and on our bodies including the skin.

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Abedon *et al.*, 2011 have carried out an extensive review of the history of phage treatment in human infections including skin infections particularly of ulcers and wound healing. Here we will focus on current phage therapy with mention of some past phage therapy in treatment of bacterial skin infections. In 1936 Gougerot and Peyre demonstrated the positive outcome of phage therapy on different skin infections, particularly furunculosis, more commonly known as 'boils', an infection of the hair follicle resulting in abscess and pus formation (Ibler and Kromann 2014). The treatment which proved most successful, (which was repeated every 48 hours for a total of 8-10 applications), involved opening the skin pustules with a syringe containing phage followed by direct application of the phage to the area, and the dressing applied also contained phage (Gougerot and Peyre 1936). They also proposed a similar method of phage therapy in the treatment of bacterial skin diseases like impetigo, a staphylococcal or streptococcal skin infection that presents in the form of red crust-like sores (Hartman-Adams, Banvard and Juckett 2014). Another early documented effective use of phage therapy in the treatment of 'suppurative skin infections' was reported by Cislo *et al.*, 1987. Here they carried out a 16-week study on 31 patients with skin infections caused by '*Pseudomonas, Staphylococcus, Klebsiella, Proteus* and *Escherichia* species. In 25 of the 31 cases, improvement on a scale from 'outstanding' to 'transitory' was reported with the former being a much higher number (16/31 cases). The phage therapy reduced inflammation, increased healing of wounds and ulcers and inhibited the bacteria in question.

Pyophage is a cocktail of phage targeting *Staphylococcus, Streptococcus, Pseudomonas, Proteus* species and E. coli used to treat skin infections (Abedon *et al.* 2011). Pyophage was first developed in 1930's and is today one of the main commercial products of Georgian Eliava Institute of Bacteriophage, Microbiology and Virology (Villarroel *et al.* 2017).

Successful phage therapy in treating Netherton syndrome (NS) was reported recently (Zhvania *et al.* 2017). NS is a rare genetic autoimmune disorder that affects the hair, skin and

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immune system with an incidence of 1/200,000 per head of population (Tran and Cohen 2012; Boskabadi, Maamouri and Mafinejad 2013). In most cases it presents as a triad of characteristics including congenital ichthyosiform erythroderma (inflamed red scaling and peeling skin), trichorrhexis invaginate (bamboo hair due to hair shaft abnormality), and atopic diathesis (predisposition to allergies) which is linked to recurring bacterial infections. NS has been linked to the genetic mutations in the serine protease inhibitor of Kazal type 5 (SPINK5) gene in the host, which plays a role in regulating skin barrier growth (Leung, Barankin and Leong 2018). Zhvania *et al.*, 2017 described the case of a 16-year-old male with NS experiencing repeated serious staphylococcal infections. Due to atopic diathesis he was allergic to many antibiotics and so phage therapy was attempted at Eliava Phage Therapy Centre. Significant improvement in his symptoms was reported within a week after treatment with a cocktail of anti-staphylococcal phage and this improvement continued during the six months of continued phage therapy at home.

C. acnes is an anaerobic bacterium found in the pilosebaceous unit of human skin. *C. acnes* is a dominant commensal skin bacterium and is thought to be a major contributing factor in skin disease acne vulgaris. Marinelli, Fitz-Gibbon and Hayes, 2012 isolated 11 *C. acnes* phage from the skin of a diverse group of people ranging in age, geographical location, healthy and acne skin. They found that the phage had a broad killing range against different *P. acne* strains. Genome sequencing revealed that the genome diversity of the phage was quite small when compared to other phage and they hypothesised that this was due to the restricted lipid rich anaerobic environment that it resides in concluding that phage therapy is very suitable candidate as a potential antimicrobial treatment for acne. Studies have described isolation of *C. acnes* phage and the ability of this phage to kill *C. acnes* (Liu *et al.* 2015a; Brown *et al.* 2016). However application of phage therapy *in vivo* in the treatment of

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acne patients is yet to be completed (Jończyk-Matysiak *et al.* 2017; Castillo, Nanda and Keri 2019).

In the Ludwik Hirszfeld Institute of Immunology and Experimental Therapy, Wroclaw, Poland, Międzybrodzki *et al.*, (2012) carried out phage therapy on 153 patients and found that phage therapy was effective in treating skin, orthopaedic, urinary and respiratory tract infections that were resistant to antibiotics. Anti-staphylococcal phages were used in treatment of these infections and while the study was performed without a control group, 36.7% of subjects reported improvements after phage therapy. It was also reported that topical application of staphylococcal phage was more effective than other types of phage treatment; 16.7% of patients with skin infections improved after topical phage therapy. Further studies should be carried out to validate the effectiveness of phage therapy as a treatment for skin infections.

Biological tools to treat skin disease indirect - via gut

Probiotics, Prebiotics, and the Gut-Skin axis

In 2001, the World Health Organisation (WHO) and the Food and Drug Administration(FDA) defined probiotics as 'live microorganisms which, when administered in adequate amounts, confer a health benefit to the host;'' a definition that was revisited and clarified by Hill *et al.*, 2015. However, we now know that dead microorganisms can also confer health benefits, as aforementioned in this review a heat-treated derivative of *Lb. johnsonii* was effective in treating AD (Blanchet-Réthoré *et al.* 2017). Many studies have shown that ingestion of probiotics influences the gut, which in turn influences the skin microbiota, further suggesting the presence of a gut-skin axis. Indeed, Levkovich *et al.*, 2013 found that feeding a probiotic yogurt containing *Lactobacillus reuteri* to aged mice affected

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their bodies via changes in skin features. The probiotic initiated an interleukin-10 dependent mechanism, which resulted in mice exhibiting increased dermal thickness and shinier fur.

After consuming the probiotic yogurt, the fitness and fertility of the mice had improved, with researchers noting an overall 'glow of health'. Rosenfeldt *et al.*, (2003) carried out a study on 43 children with AD, average age 5.2 years, and showed that ingestion of combination probiotic of *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460 improved symptoms of eczema. Rosenfeldt et al., continued this study and demonstrated that the same probiotic combination alleviates both small intestine permeability and gastrointestinal symptoms (Rosenfeldt *et al.* 2004). Kim et al. show how administration of a probiotic cocktail of *Bifidobacterium bifidum*, *Bifidobacterium lactis*, *Lactobacillus acidophilus* to pregnant women can confer a protective effect against development of eczema in high risk infants in their first year of life. They conducted a study where 112 pregnant women with a family history of allergy disorders were divided into two groups: one group given a probiotic mix and the other given a placebo. The incidence of eczema was significantly lower among infants whose mothers took the probiotic mix compared to mothers who took the placebo however exposure to common food allergens did not result in differences in IgE levels (Kim et al., 2010).

A prebiotic on the other hand is currently defined as 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' (Gibson et al., 2017). Prebiotics are indigestible oligosaccharides that promote beneficial bacteria to colonise the gut (Ashwini *et al.* 2019). Bateni *et al.*, 2013 demonstrated how Konjac Glucomannan Hydrolysates (GMH), a prebiotic, could be used as a novel topical therapy. Twenty-six females with acne lesions between the ages of 18-39 were treated with either generic antibiotic or a topical prebiotic spray of GMH, both treatments significantly ameliorated in skin health. Contact hypersensitivity (CHS) can result in a very common skin diseases: allergic contact dermatitis

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(ACD) (Mowad *et al.* 2016). Watanabe *et al.*, (2008) demonstrated that ingestion of the prebiotic fructo-oligosaccharide (FOS) increased the numbers of intestinal *Bifidobacteria pseudolongum* which in turn reduced ear swelling (CHS), that was induced by 2,4-dinitrofluorobenzenein mice.

Other examples of biotherapeutic potential of skin commensals

Anti-skin cancer

It has been recently reported that some strains of the human commensal *S. epidermidis* produce a molecule that inhibits DNA polymerase, called 6-N-hydroxyaminopurine (6-HAP), and can protect against skin neoplasia. Nakatsuji *et al.*, 2018 demonstrated that by injecting mice with 6-HAP, the growth of melanoma was stopped. They also showed that mice colonised with 6-HAP producing *S. epidermidis* strains did not develop as many tumours as mice colonised with a non-6-HAP producing control strain, when exposed to ultra-violet radiation. No evidence suggesting damage to either keratinocytes or system toxicity by 6-HAP was observed. With further clinical studies this could be a novel biological treatment of skin cancer.

Novel antibiotic

Zipperer *et al.*, 2016 discovered a new ‘’thiazolidine-containing cyclic peptide’’ antibiotic ‘lugdunin’ produced by human commensal *S. lugdunensis*, isolated from the nose of human subjects, that inhibited growth and establishment of *S. aureus.* Lugdunin also displayed inhibitory activity against other major pathogens including some streptococci, enterococci, listeria. Lugdunin has potential for future use in tackling staphylococcal infections.

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Probiotics in wound healing

Pseudomonas aeruginosa is a Gram-negative bacterium that has many associations with the pathogenesis of cystic fibrosis (Davies 2002), it is however also implicated in burn-wound sepsis (Kim *et al.* 2015). Argenta *et al.*, (2016) created a burn-sepsis mouse model incorporating *P. aeruginosa* and demonstrated that application of probiotic bacteria *Lactobacillus plantarum* to the burn greatly reduced mortality rates of mice when compared to untreated model- 90% as opposed to 10%. This suggests an approach to treating wounds without use of antibiotics. Recently Li *et al.*, 2019 presented a potential candidate, a strain of *S. epidermidis* for future wound treatment. They demonstrated *in vivo* how *S. epidermidis* modulated skin inflammation by producing Lipopeptide 78 (LP78), which in turn inhibited TLR3-mediated inflammation, promoting wound healing.

Conclusion

While the extent of the role human skin commensals play in skin health and disease remains to be fully understood, it is apparent that like the gut, diversity and balance of bacterial communities is vital for skin health. It's clear that our skin's residents' function in many ways and there is a wide variety of biological tools with the capability of manipulating the skin microbiota in play. Understanding how cutaneous microbiota modulate skin disorders is key to developing novel skin therapeutics (Paller *et al.* 2019; Sun *et al.* 2019). The global emergence of antimicrobial resistance (AMR) is posing a threat to human health (WHO Global antimicrobial resistance surveillance system report: early implementation 2017-2018), and therefore more attention is being paid to novel alternative therapies with potential to decrease the use of antibiotics worldwide. With huge antimicrobial potential apparent, it is

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essential to further develop these biological tools into therapeutic products for the treatment of skin related and other diseases. However, before these tools will be fully exploited there are many areas that will require further studies including evaluating potential associations of skin microbiota with health and disease using molecular approaches, and elucidation of mechanisms of action to tease out signalling pathways. What role does the brain play in signalling from gut to skin? Larger *in vivo* based human trials are required to determine whether biological tools such as probiotics, prebiotics, bacteriocins and phage can be used as primary prevention or treatment options for skin diseases.

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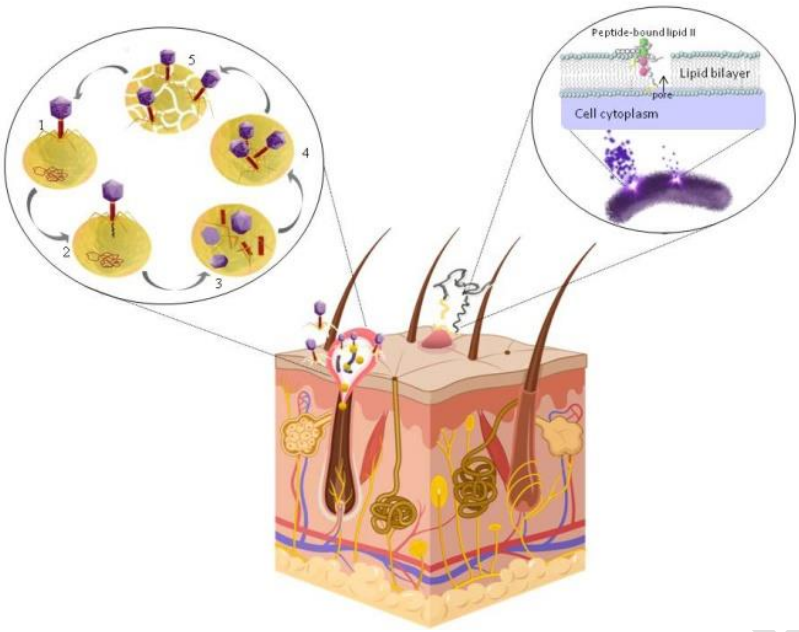


Figure 1: illustration of non-antibiotic strategies including phage and antimicrobial peptides acting on human skin, created with BioRender.

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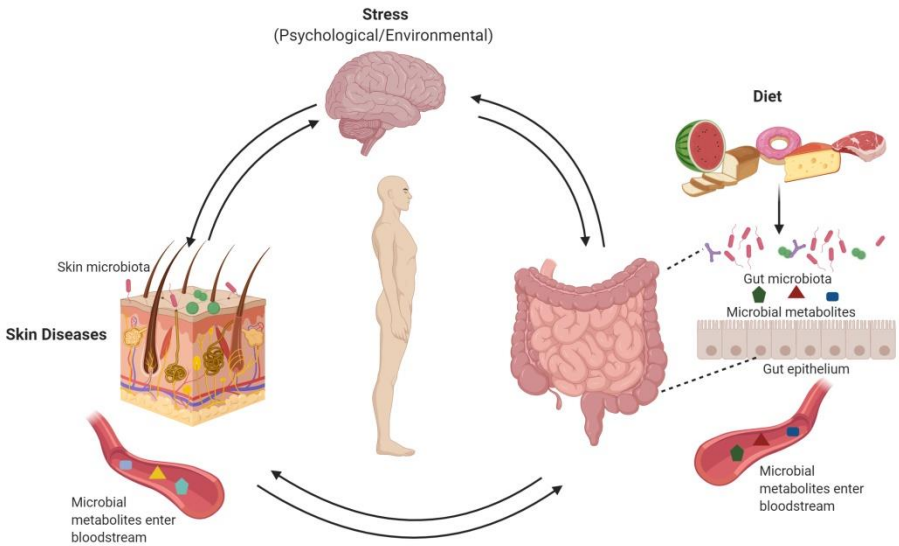


Figure 2: illustration depicting the gut- skin- brain connection, created with BioRender.

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Skin disease	Characteristic	Associated with	Current treatment	Novel treatment
Impetigo	blister-shiny or crusted lesions	*Staphylococcus aureus*, *Streptococcus pyogenes*	systemic and topical antibiotics	Ozenoxacin, a novel quinolone antibiotic (Sahu and Mishra, 2018)
Atopic dermatitis	red, itchy dry skin patches	*Staphylococcus aureus*	topical corticosteroids and antibiotics	topical probiotic lotion containing a heat-treated strain of *Lactobacillus johnsonii*(NCC 533) (Blanchet-Réthoré *et al.*, 2017)
Acne vulgaris	whiteheads, blackheads or pimples, lesions or scars	*Cutibacterium acnes* type1A	topical benzoyl peroxide or salicylic acid, topical antibiotic, topical and oral retinoids	Myrtacine® ; (Pécastaings *et al.*, 2018)
Psoriasis	Red patches of skin covered with thick, silvery scales.	*Corynebacterium*, *Propionibacterium*, *Staphylococcus*, *Streptococcus* species	topical corticosteroids, vitamin D analogues, topical retinoids and coal-tar	immunotherapy focused
Cutaneous leishmaniasis	erythematous papule that develops into an ulcer with a raised and distinct border	*Staphylococcus* *Streptococcus* species	-	Amphotericin B; (Mushtaq, Dogra and Dogra, 2016)

Table 1 Summary of characteristics and microbes associated with skin diseases, as well as current and novel treatments

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Biological tool		Producer	Host range	Molecular weight	Mode of action	Reference
Name	Type					
Gallidermin	bacteriocin	*Staphylococcus gallinarum*	broad	>5kDa	Peptides that disrupt membranes resulting in cell death*	Shi et al., (2015); Bonelli et al., (2006); Kellner et al., (1988)
Epidermin	bacteriocin	*Staphylococcus epidermidis*	broad	>5kDa	*same as above	Götz et al., (2014); Kellner et al., (1988); Bonelli et al., (2006)
Hominicin	bacteriocin	*Staphylococcus hominis*	*S. aureus* MRSA, VISA**	>5kDa	*same as above	Sung et al., (2010); Kim *et al.*, (2010)
Nukacin ISK-1	bacteriocin	*Staphylococcus warneri*	broad	>5kDa	*same as above	Kimura et al., (1997); Sashihara et al., (2000) Asaduzzaman et al., (2009)
Pyo-phage	bacteriophage	-	broad	>100kDa	Virus that infects bacteria	Abedon et al., (2011)
Lugdunin	antibiotic	*Staphylococcus lugdunensis*	broad	<2000Da	immuno-modulatory bactericidal activities	Zipperer et al., (2016); (Bitschar *et al.*, 2019)
SCFA	-	Fermentation of skin commensals	*Cutibacterium acnes*, MRSA	60-102 g/mol	protects against pathogens by increasing acidity of skin	Wang et al., (2014), Shu et al., (2013)
PSMγ & PSMδ	PSM	*Staphylococcus epidermidis*	*S. aureus*& group A streptococci	~2kDa	Cell membrane disruption, resulting in cell death	Cogen et al., (2010) and Cogen, Yamasaki, Muto, et al., (2010)

Table 2 Examples of biological tools and their mode of action **VISA= Vancomycin intermediate *Staphylococcus aureus*

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