The Skin Microbiome: KMINE text mining suggests important skin microbiome modulators

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Introduction

Shotgun metagenomic sequencing and subsequent bio-informatics analysis pipelines reveal the composition of the skin microbiome and its players on species- and strain level. It remains, however, a challenge to determine functionalities of these players and their link to disease. This is essential knowledge needed to find promising cures.

This whitepaper shows how two TenWise text mining products: **KMINE Literature Report** and **KMINE Literature Explorer**, address this challenge. We identify the relation between the organisms in the skin microbiome and skin diseases and we suggest different intervention strategies that can reduce the effect of the pathogenic ones.

KMINE Literature Report: relations with important skin disorders

We have taken the main bacterial players in compromised skin from Nature Review 'The human skin microbiome' by Allyson L. Byrd, Yasmine Belkaid & Julia A. Segre (2018), that used shotgun metagenomics to identify the species in a diverse set of habitats.

Based on the top 25 players we generated a **KMINE Literature Report** that can be found on: https://www.tenwiseapps.nl/clientportal/public/skinset.html. Here relations between 25 skin commensals and important skin diseases, skin disorders, phenotypes and pathways related to skin (eg. desquamation, wound healing, ceramide signaling) are given. Table 2 is an extract from the report that displays the hyperlinked numbers of available literature in which both a species and a skin disease/phenotype co-occur, ranked from high to low. The hyperlink itself links to the TenWise server showing all related abstracts with both concepts highlighted.

Table 1: Ranked overview of hits between bacterial species on the skin and skin diseases/phenotypes.

Species	Skin disease/phenotype	Number of hits	Species	Skin disease/phenotype	Number of hits
Staphylococcus aureus	dermatitis	1204	*Staphylococcus aureus*	pruritus	100
Staphylococcus aureus	wound healing	997	*Staphylococcus epidermidis*	wound healing	95
Cutibacterium acnes	acne vulgaris	980	*Pseudomonas aeruginosa*	dermatitis	87
Staphylococcus aureus	atopic dermatitis	972	*Staphylococcus aureus*	fatty acid metabolism	82
Pseudomonas aeruginosa	wound healing	486	*Staphylococcus aureus*	desquamation	78
Staphylococcus aureus	Skin rash	306	*Pseudomonas aeruginosa*	ceramide	71

Staphylococcus aureus	acne vulgaris	145	*Staphylococcus epidermidis*	dermatitis	64
Staphylococcus aureus	psoriasis	133	*Streptococcus pneumoniae*	Skin rash	62
Corynebacterium xerosis	Dry skin	130	*Staphylococcus aureus*	ceramide	62
Pseudomonas aeruginosa	Skin rash	127	*Cutibacterium acnes*	dermatitis	59
Staphylococcus epidermidis	acne vulgaris	101	*Pseudomonas aeruginosa*	fatty acid metabolism	57

From this table one can extract the species that are most and most often involved in skin health and skin disorders. These target species are:

- ***Staphylococcus aureus:***
  Clearly negatively linked to **(atopic) dermatitis** and **wound healing**, **skin rash** and **desquamation** but also to **acne** and **psoriasis**. *S. aureus* has been linked to T-cell dys-function, reduced AMPs, more severe allergic reactions and disruptions in the skin barrier (Nakatsuji *et al.*, 2018).

- ***Cutibacterium acnes*:**
  Both strongly negatively and positively linked to **acne** and to a lesser extent to **dermatitis.** Its bipolar role is described as: 'While the commensal bacterium *Propionibacterium acnes* (*P. acnes*) is involved in the maintenance of a healthy skin, it can also act as an opportunistic pathogen in acne vulgaris.' (Dreno *et al*., 2018)

- ***Staphylococcus epidermidis*:**
  Mostly negatively linked to **acne** as being a 'pus forming bacterium', but often mentioned positively in relation to: **wound healing** and **dermatitis: '***Staphylococcus aureus* (*S. aureus*) is one of the well-known agents causing atopic dermatitis (AD) in susceptible individuals, and *Staphylococcus epidermidis (S. epidermidis*) produces class I thermostable bacteriocins that can selectively kill *S. aureus*, suggesting protective roles against AD' (Jang *et al.*, 2020). '*S. epidermidis* also produces phenol-soluble modulins … which have direct antimicrobial activity against *S. aureus* and activate toll-like receptor 2 (TLR2) on keratinocytes, leading to production of CAMPs … which amplify the immune response and promote killing of *S. aureus*." (Cogen *et al*., 2010).

- ***Pseudomonas aeruginosa***:
  Negatively linked to **wound healing and skin rash.** '*Pseudomonas aeruginosa* motility, virulence factors and biofilms are known to be detrimental to wound healing.' (Guoqi *et al.*, 2018)

These outcomes confirm that functionalities of these four identified target strains are superficially described in available literature having a predominantly detrimental effect on skin health. Reduction of these pathogens seems a strategy to reduce the occurrence of mentioned skin disorders.

So, what therapeutic interventions are currently clinically tested and suggested in literature?

KMINE Literature Explorer: identification of potential interventions

Our **KMINE Literature Explorer** classifies available literature into evidence categories. Here we show potential interventions from recorded and planned clinical trials that have a microbiome focus.

The potential is described below:

- **Live Biotherapeutic Product (LBP):**
  Limited evidence is described in literature to date for the potential use of skin derived commensal bacteria as Live Biotherapeutic Products. *Staphylococcus epidermidis* subspecies are described as potential candidate for treatment of skin disorders as it excretes antimicrobial peptides (AMPs) that can reduce/kill pathogenic *C. acnes* and *S. aureus* strains. Other skin derived subspecies that report a similar antimicrobial effect on skin pathobionts for different diseases are: *S. hominis*, *S. capitis* and *C. acnes* (combined work by R.L. Gallo), an engineered *S. epidermidis* strain (Dodds *et al.*, 2020) and *C. acnes* H1 strain's capacity for modulation of the skin microbiome in sebaceous glands of a healthy population (Paetzold *et al.*, 2019). Clinical studies now need to be performed to show beneficial effects.

- **Topically applied probiotics:**
  Non-commensal topical probiotics have been tested to date in human pilot studies with limited number of patients including *S. thermophilus* (Di Marzio *et al.*, 2003) that showed some improvement in ceramide levels and scaling, *L. reuteri* (Butler *et al.*, 2020) of which acceptability and safety has been shown in AD patients and *L. plantarum* (Lebeer *et al.*, 2018) that shows relieving effects on acne patients. In a recent clinical study, a live *Roseomonas mucosa* strain (Myles *et al.*, 2020) was topically administered to young children with AD and that induce TNF-related epithelial repair of the skin that lasted for 8 months after treatment.

- **Postbiotics:**
  Lysates and supernatants from mainly lactobacillus strains haven been tested for their topical antimicrobial effect in the clinic. Extracts from *L. plantarum* (Muizzuddin *et al.*, 2012) are clinically effective for skin barrier repair. And two clinical studies show reduction of *S. aureus* colonisation in Atopic Dermatitis patients: one by a heat-killed *L. johnsonii* (Blanchet-Réthoré, 2017) and the other by a lysate of *V. filiformis* (Gueniche *et al.,* 2008).

- **Other interventions:**
  Recent examples of interventions with different substances than those described above are: Omiganan, an indolicidin with antimicrobial properties show small but statistical improvement of clinical outcomes in AD patients (Niemeyer-van der Kolk *et al.*, 2020) and a topical application of a substance of 1% colloidal oatmeal that improves skin barrier and skin hydration in AD patients (Capone *et al.*, 2020). A 2019 study using bacteriophage derived endolysins by De Wit *et al.* (2019) aimed to show topical steroids sparing effects (no abstract available).

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Conclusions:

- KMINE Literature Reports **give fast insight** in the bacterial species within the skin microbiome that are most described in relation to skin disorders of which the main are: acne, (atopic) dermatitis and wound healing. The main pathogenic subspecies implicated in these skin diseases are *C. acnes*, *S. aureus, S. epidermidis* and *P. aeroginusa*.

- KMINE Literature Explorer analyses **suggest evidence** available in recorded and suggested clinical trials with microbiota analyses, for the use of modulators that can reduce these target pathogens. Showing potential are:
    - **Live Biotherapeutic Products (LBPs)** that consist of beneficial subspecies of amongst others *S. hominis*, *S. epidermidis* and *C. acnes*. These are drug candidates under development.
    - **Topically applied probiotics,** mostly (sub)species of *Lactobacillus*, that show first proof of concept effect in humans. Larger clinical trials are suggested.
    - **Postbiotics** such as supernatants and lysates derived from mainly (sub)species of *Lactobacillus*, that have been clinically tested and are already applied in commercial cosmetic products.
    - **Other interventions** such as purified antimicrobial peptides and bacteriophage derived endolysins currently being tested in clinical trials.

Disclaimer: The microbiome consists not only of bacteria, but also fungi and yeasts that are likely to play a role in skin health. This whitepaper focuses on bacterial players only.

About TenWise

TenWise B.V. is set-up by Wynand Alkema PhD and Nils Hijlkema MSc who have a combined experience of over 35 years in food and life sciences research.
They have been active in drug discovery, microbiome and probiotic programs in both industrial and academic settings. Dr. Alkema is also Professor of Data Science at Hanze University of Applied Sciences in Groningen.

TenWise offers text mining solutions by providing access to its KMAP platform via its KMINE Literature Explorer, the KMINE REST-API solution and a fast service for generating KMINE Literature Reports.

The company is based in Leiden, the Netherlands and works for clients around the world.
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