

Past, present and future of 'microbiome skincare'



Agenda

Past: History and science of probiotic lysates for cosmetics

Present: Linking probiotic lysates with the skin microbiome

Future: Influencing the skin microflora with cosmetic products



Past:

History and science of
probiotic lysates
in the cosmetic industry



Bifida ferment lysate

First patent applied for in 1981

United States Patent [19]

Kludas et al.

[11] Patent Number: 4,464,362

[45] Date of Patent: Aug. 7, 1984

[54] TOPICAL SKIN REPAIR COMPOSITION

[75] Inventors: Martin Kludas; Dieter Heise, both of Berlin, Fed. Rep. of Germany

[73] Assignee: Estee Lauder Inc., New York, N.Y.

[21] Appl. No.: 355,579

[22] PCT Filed: Jan. 26, 1981

[86] PCT No.: PCT/EP81/00686

§ 371 Date: Feb. 23, 1982

§ 102(e) Date: Feb. 23, 1982

[87] PCT Pub. No.: WO82/00093

PCT Pub. Date: Jan. 21, 1982

[30] Foreign Application Priority Data

Jan. 27, 1980 [DE] Fed. Rep. of Germany 3024318

[51] Int. Cl.² A61K 35/74

[52] U.S. Cl. 424/195; 424/95

[58] Field of Search 424/92, 93, 94, 95,
424/177, 180, 195

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[57] ABSTRACT

Cosmetic compositions containing an active substance complex for promoting the DNA repair process of the skin cells, in order to guard against possible cellular skin damage due to excessive light influence, and to counteract the light-caused aging process of the skin. The active substance complex consists of inactivated cultures of bacteria of the genus *Bifidobacterium* or bacteria related to this genus.

20 Claims, No Drawings



Science relevant to 'anti-photogaging' properties

Presented:

Stimulation der Repair-Synthese gegen bleibende DNA-Schäden

W. Born, A. L. Born und M. Kludas, Freiburg und Berlin

Material und Methode

Als Untersuchungstechnik wurde die Tritium-Thymidin-Histoautoradiographie gewählt, welche Repairsynthesen am Ort ihres Ablaufs in der Zelle markiert. 15 Minuten nach einer zweitägigen Vorbehandlung der gesunden Rückenhaut von 7 Erwachsenen im Alter von 30 bis 76 Jahren mit jeweils 0,05 ml einer allgemein leicht erhältlichen **CLR-Repair-Creme mit 10% Wirkstoffkomplex aus inaktivierten Kulturen der Gattung Bifidobacterium** als O/W-Emulsion unter Testpflaster (Finn Chamber) erfolgte die experimentelle DNA-Schädigung durch das erythemwirksame ungefilterte Ultraviolettlicht einer Xenon-Hochdruck-Quarzlampe (Osram XBO 150 W) für die Dauer von 60 Sekunden bei 19 cm Abstand von der Lichtquelle und Fokussierung mittels Quarzlinse auf 2 m, entsprechend einer Dosis um 8 MED, welche die nach Howard-Flanders [3] maximal mögliche Reparaturantwort auslöst (Abb. 1, *Feld A*).

So ergibt sich insgesamt die Feststellung, daß die Repair-Creme CLR eine augenscheinlich sehr gut hautverträgliche Substanz ist, welche die limitierte individuelle DNA-Reparaturfähigkeit erheblich zu steigern vermag [2].



More recent science

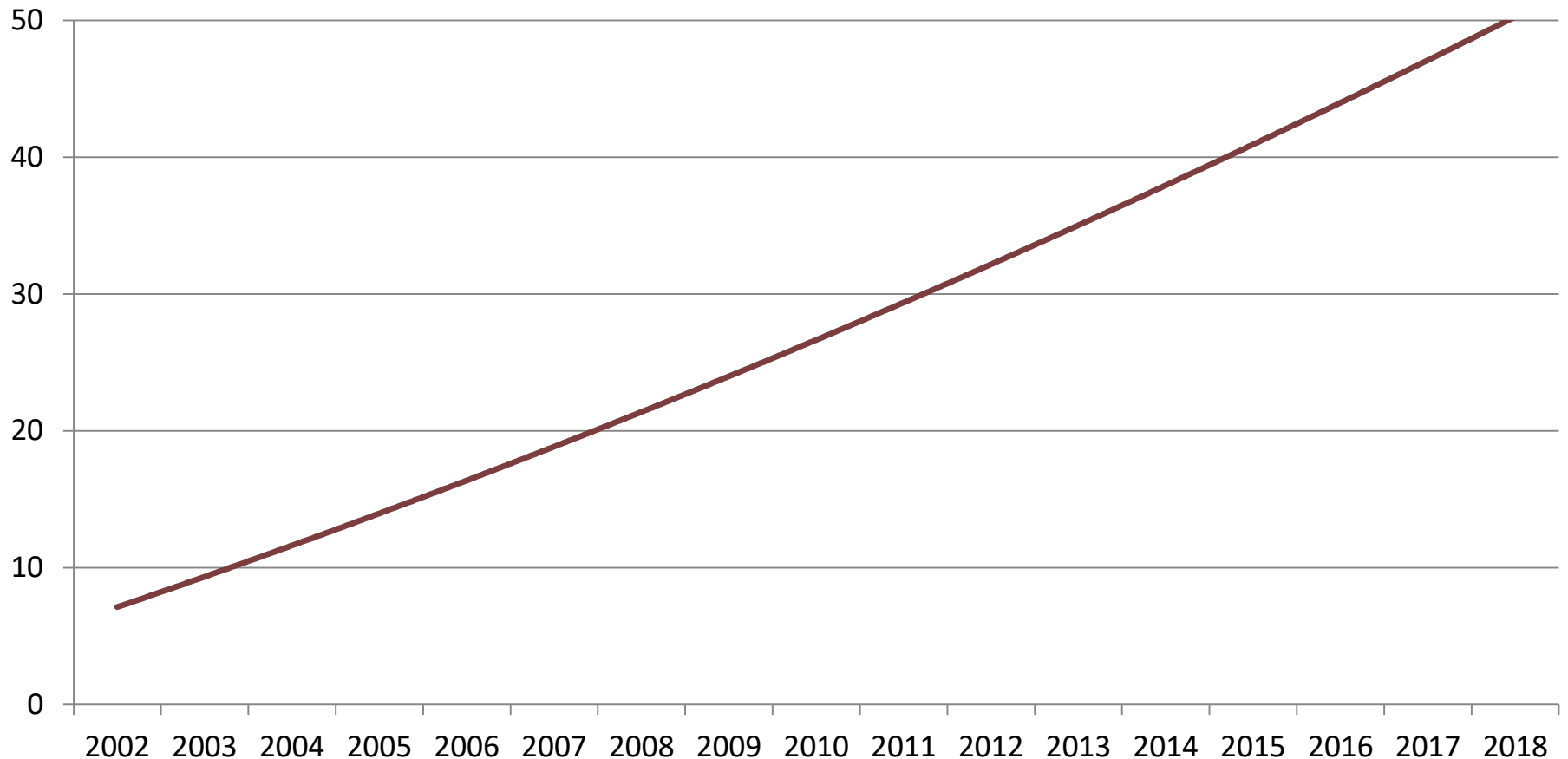
Lucas CR et al, 'Immune protective effect of a moisturizer with DNA repair ingredients', Journal of Cosmetic Dermatology, 2008, Vol. 7, 132–135

72 h later. The DNA repair concentrate is a proprietary, amplified combination of cellular repair ingredients including Bifidus (micrococcus lysate) Bifiderm+ (50% proline-rich glycoprotein fraction of soy) and RNA fragments encapsulated in liposomes.

This study therefore suggests that a commercially available DNA repair concentrate applied after UV radiation prevents UV-induced immunosuppression. Although



Bifida Ferment Lysate: an established active ingredient



Mintel GNPD: number of brands vs date launched (trend)
(estimated: x10 brands not in GNPD database)



Bifida ferment lysate for reactive skin

Guéniche A et al, 'Bifidobacterium longum lysate, a new ingredient for reactive skin', Experimental Dermatology, 2010, Vol.19, e1–e8

Materials and methods

Bacterial extract

Bifidobacterium longum reuter lysate (BL) is an ultrasound inactivated suspension in aqueous medium. This strain has the following INCI code: Bifida ferment lysate. The active form is at 5% in the total suspension

The results of the various efficacy studies conducted on BL lysate demonstrate that after topical application, a specific bacterial lysate or extract may cause a beneficial effect on skin [i.e. decreasing skin sensitivity, increasing resistance of skin barrier, maintaining moisturizing factor concentrations in the skin (urea)]. Since various studies show that in the presence of bacterial extract, isolate sensitive neurones release less CGRP under capsaicin stimulation, a reduced inflammatory response is observed under SP stimulation and skin resistance to tape stripping is improved, we speculated that this new ingredient may decrease clinical sensitive skin reaction by reducing neurones reactivity and neurones accessibility to external stimuli.



Bifida ferment lysate for 'skin health'

Szöllősi AG et al, 'Bifidobacterium longum extract exerts pro-differentiating effects on human epidermal keratinocytes, in vitro', Experimental Dermatology, 2017 Jan;26(1):92-94

5 | CONCLUSIONS

The intriguing findings of this study provide the first evidence that certain *B. longum* extract preparations exhibit significant pro-differentiating and potentially pro-regenerating (cathepsins' expression) actions in NHEKs, together with an increased expression of BDEF, one key actor of cutaneous innate immune response. In the single available previous study, various probiotics (certain *B. longum* and *Lactobacillus* strains) were shown to increase the expression of multiple tight-junction proteins of NHEKs and enhanced barrier function (a decreased transepidermal water loss).⁹ These data, therefore, collectively suggest that the beneficial effects of topical microbial formulations derived from bacteria may be mediated, at least in part, by direct modulation of epidermal keratinocytes' differentiation, most probably via inducing Ca^{2+} influx.



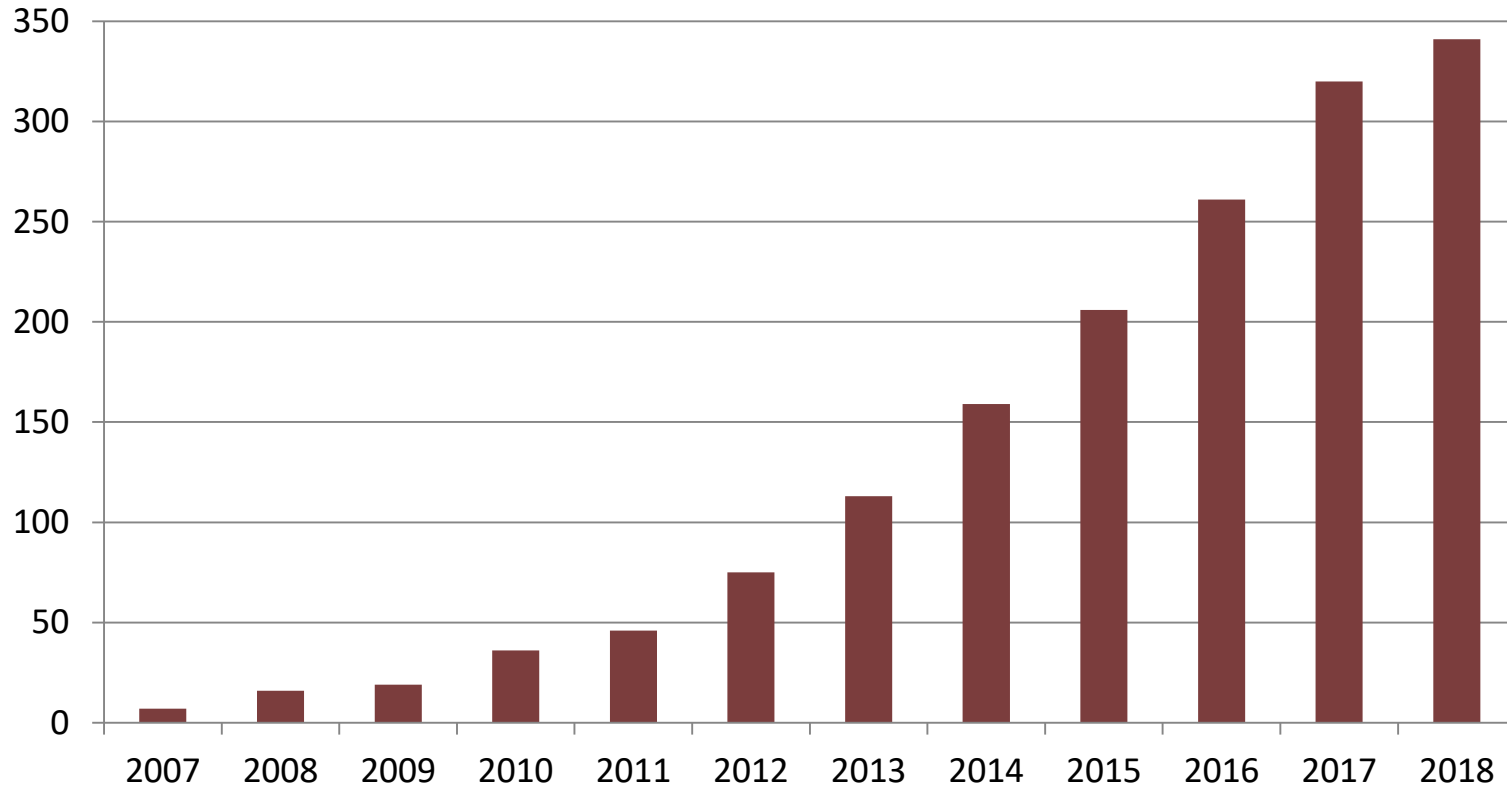
Present:

Linking probiotic lysates with
the skin microbiome



The skin microbiome: a new science

Number of scientific publications in PubMed, related to skin microflora,
2007 – 2018 (10th October) (mainly related to skin diseases)



Start of human
microbiome project



The skin and its microbiome interact

Functionality of skin is essential:

- during epidermal differentiation, ingredients' are produced which favor a healthy skin microbiome (AMPs, pH etc.)
- where these processes are disturbed the skin microbiome alters in composition

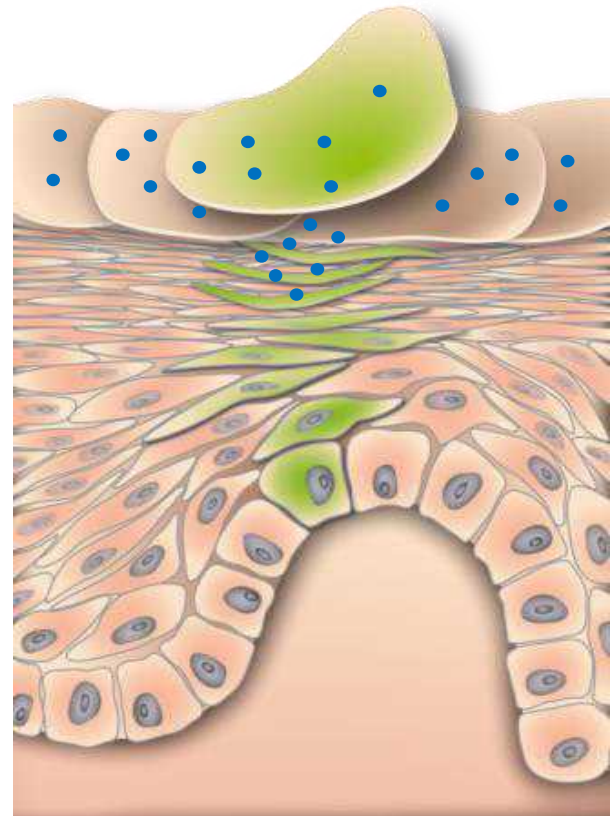
On the other hand:

skin microbes actively work on maintaining an environment favorable to their survival via interactions with the skin



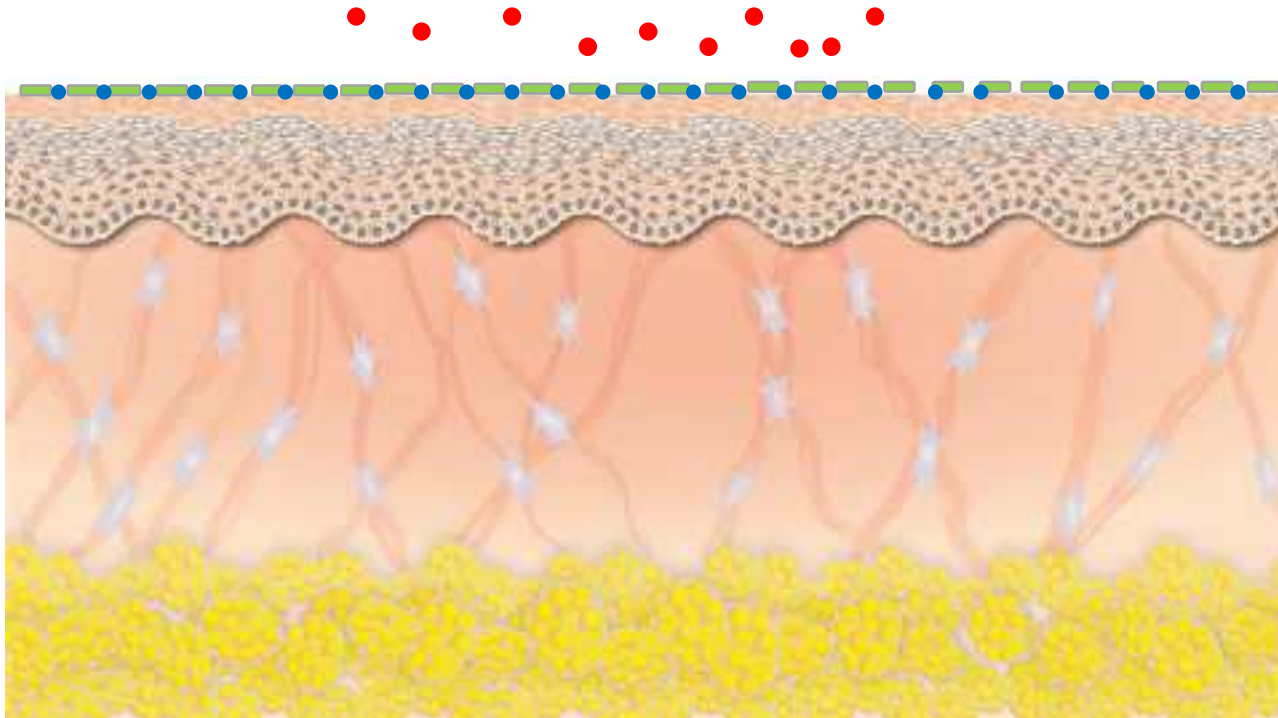
A symbiotic homeostasis

A positive feedback loop: both profit from each other



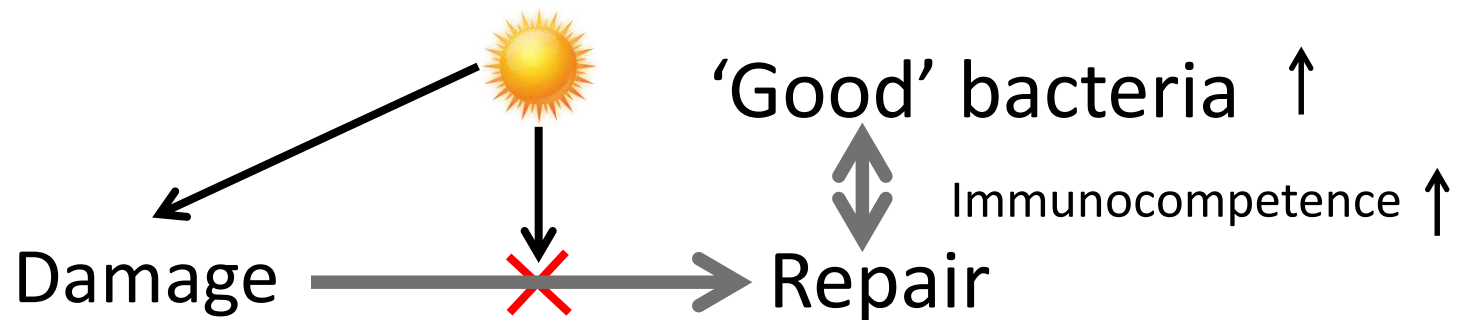
Co-operation against the colonization of bad bacteria

Commensal 'good' bacteria co-operate with skin against invasion of pathogens



The skin microbiome and UV-induced immunosuppression

- UV-light damages skin cells and prevents them repairing their damage
- The skin microbiome has a 'probiotic' immunostimulating effect compensating for this



The skin microbiome and 'skin health'

Application of skin microflora from a healthy individual onto full skin models ('physiological') leads to

- Acceleration of skin renewal
- Improvement of epidermal differentiation
- Higher cohesion between keratinocytes
- Improvement of desquamation



(application of *S. epidermidis* alone leads to disruption of the epidermis)

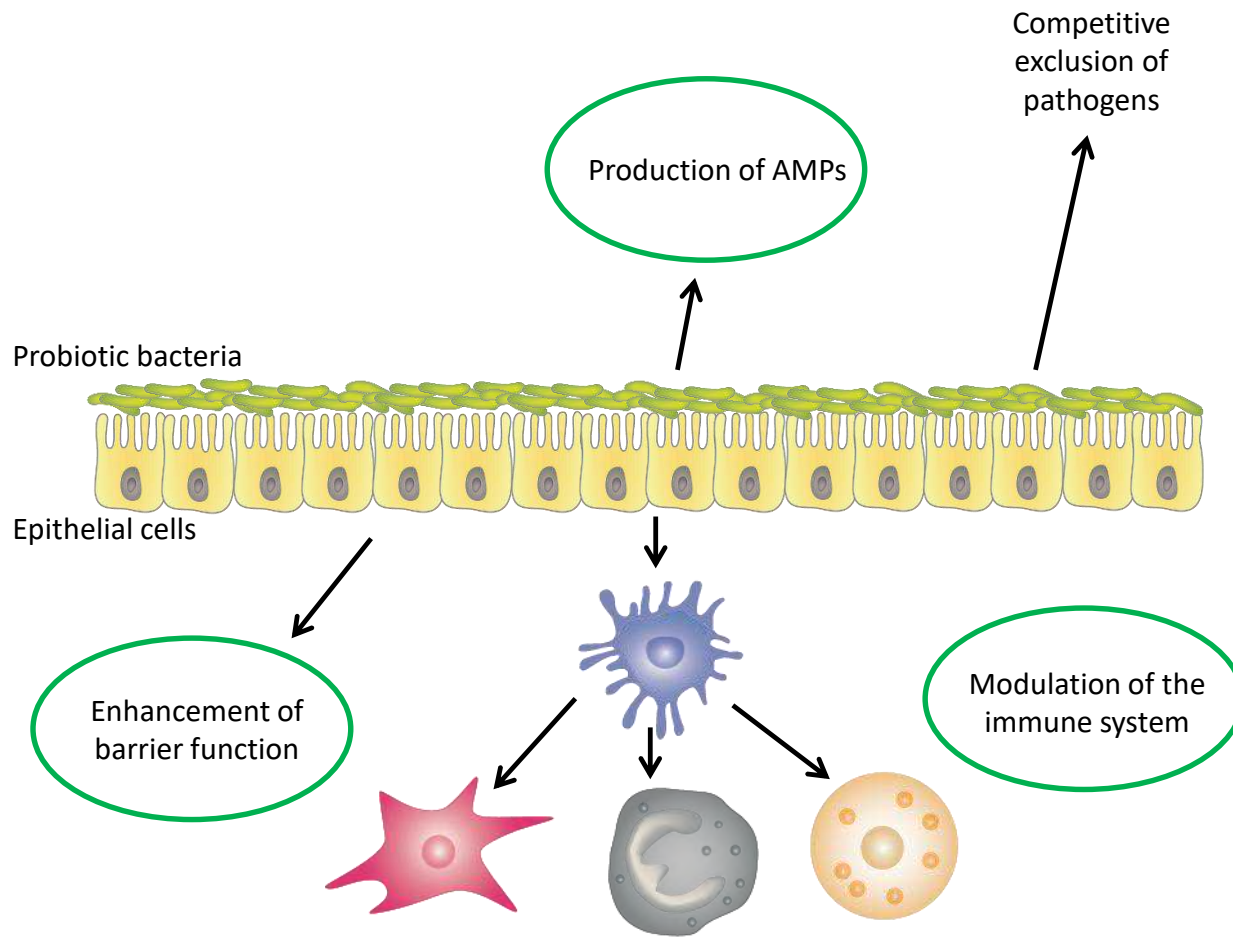
(presented by L'Occitane at IFSCC 2018)



Analogy with probiotic
bacteria in the gut:
exceptional



Probiotic bacteria in our gut



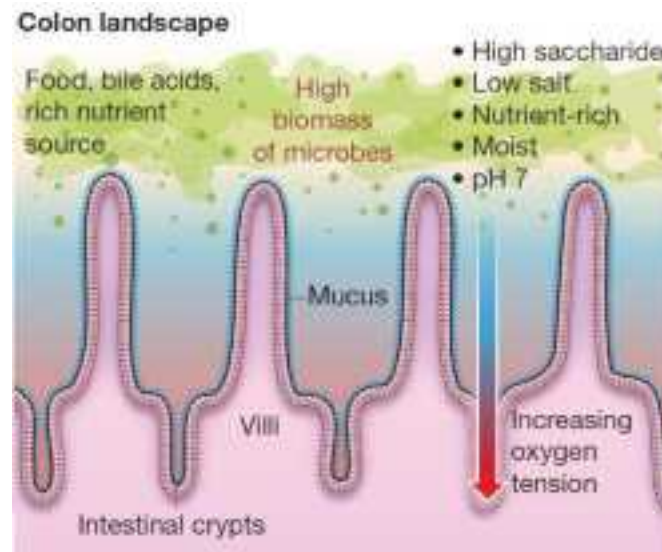
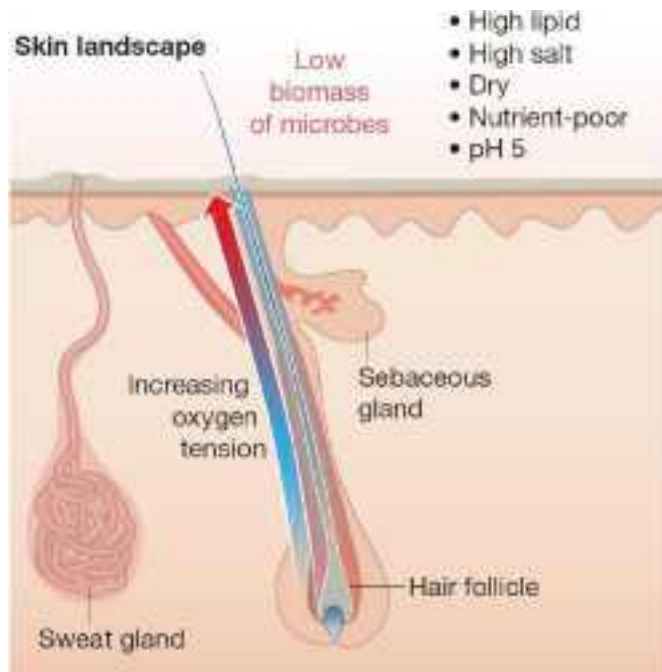
‘Healthy’ skin microbiome plays an identical role

Mechanism:
‘effector molecules’ from bacteria interact with human cells (only partly understood)



Observations - 1

1. Keratinocytes and epithelial cells in the gut play largely identical roles (physical and immunological barrier)
2. Different environments, therefore different microflora, but many overlapping ways of interaction with human cells (e.g. Toll-like receptors, short chain fatty acids, more research needed)

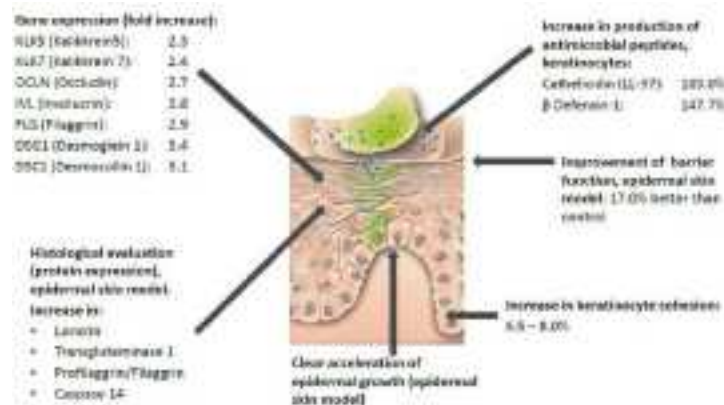


From: 'Skin microbiota–host interactions', Chen YE et al., Nature, 2018, Vol. 553, 427–436.



Observations - 2

3. Topical probiotic lysates provide bacterial effector molecules to keratinocytes (from cell surface and from intracellular compartment)
4. Studies show that probiotic lysates provide epidermis with the means to optimise its functionality. Outcomes:
 - a. Improvement of differentiation and skin's ability to manage its microbiome (e.g. antimicrobial peptide production)
 - b. Modulation of the skin's immune competence (the ability to deal with stresses ('anti-inflammatory'), the ability to deal with immunosuppression by UV ('anti-photoaging'))



Another view point: Biomimicry

Topical probiotic lysates seem to ‘mimic’ a healthy skin microbiome

“compensation for skin problems which may occur when the skin microflora is out of balance”



Future:

Influencing the skin microflora
with cosmetic products



The starting point: unavoidable influences

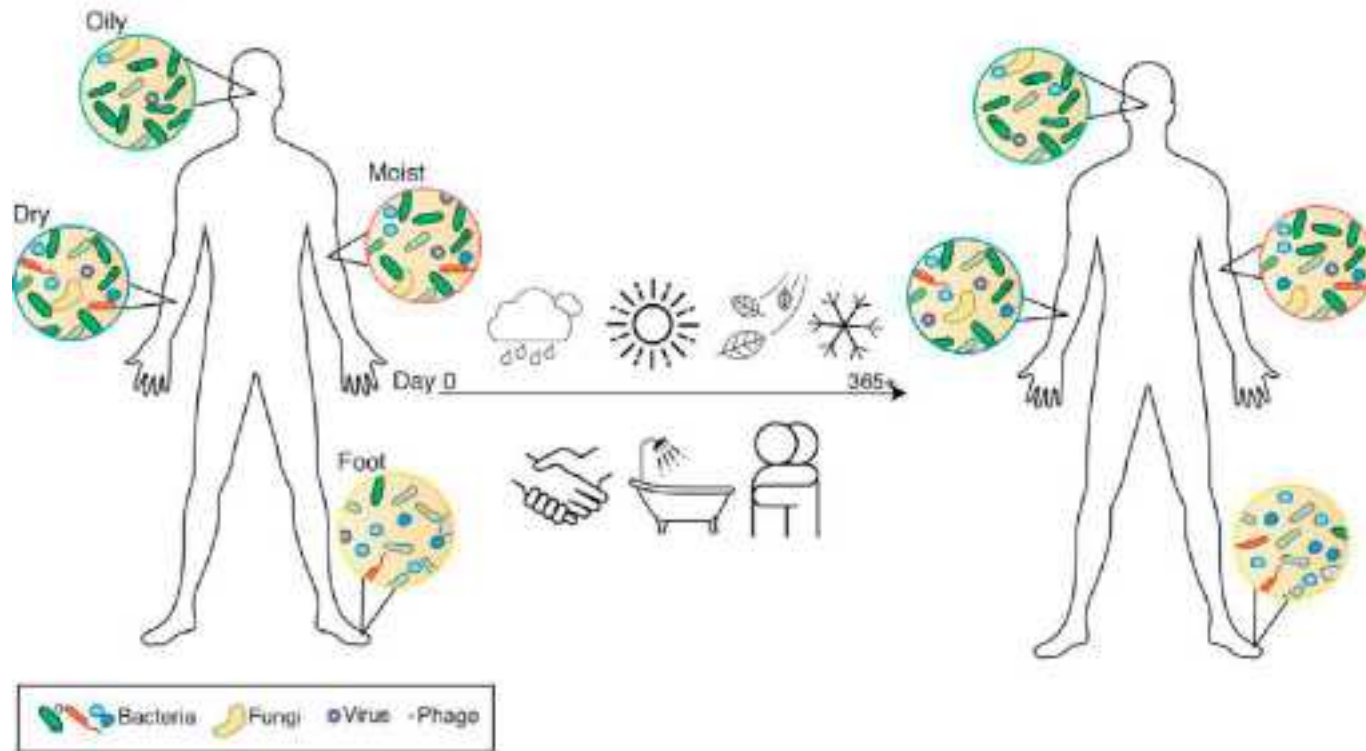
e.g.

- personal hygiene: will wash away microbes
- exposure to preservatives from cosmetics: can kill microbes
- pH of cosmetics: can favor growth of specific bacteria and reduce growth of others
- our environment and people we get in contact with: we 'adopt' bacteria from others
- shaving, clothing, abrasion
- desquamation: shedding of dead skin cells implies shedding of skin flora ("each squame is carrying a mean of four germs")

How do these impact the skin microbiome?



The skin microbiome: stable



From: 'Temporal Stability of the Human Skin Microbiome', Oh J, et.al., Cell, 2016, Vol. 165, 854-66

Long term, goal oriented anti-microbial approaches – implications and lessons

Example: anti-perspirants and deodorants

Arch Dermatol Res
DOI 10.1007/s00403-014-1487-1

ORIGINAL PAPER

Deodorants and antiperspirants affect the axillary bacterial community

Chris Callewaert · Prawira Hutapea ·
Tom Van de Wiele · Nico Boon

The autochthonous community was generally able to recover completely after the changed situation. This suggests that the community of the deeper layers of the skin returns when the situation is again favorable. Research has shown that bacteria are present in the dermis and the dermal adipose of the human skin [25]. These findings support that the bacteria in the sweat glands, around the hair roots and deeper in the epidermis are important as indigenous host microbiome [33].

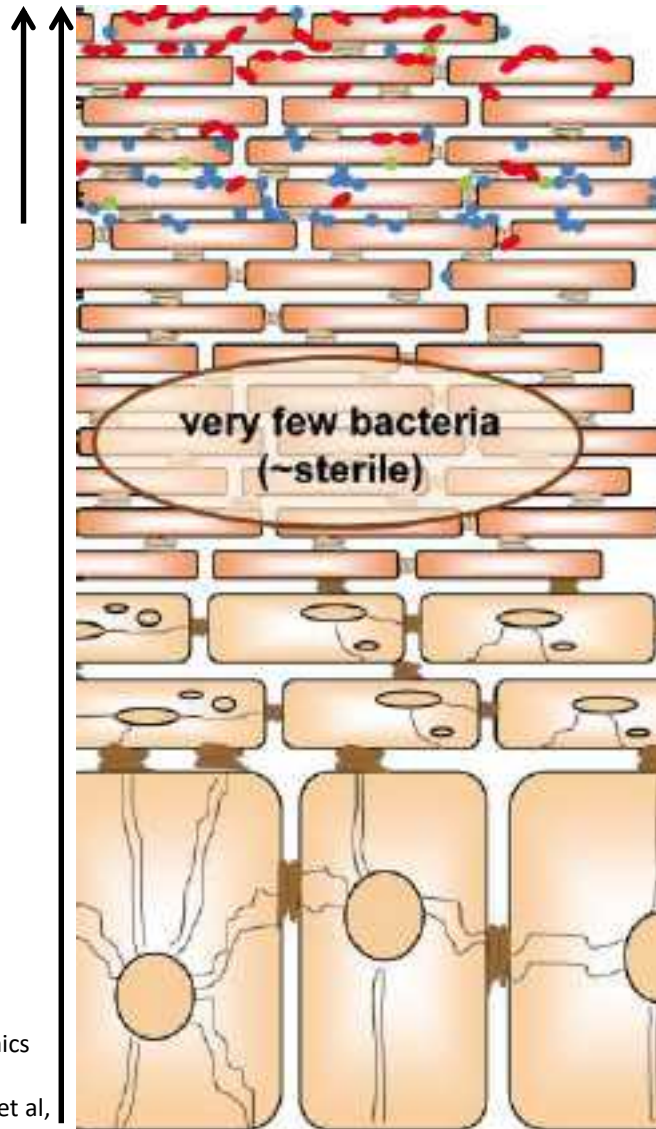


Epidermis and its flora 'renew' together

Skin cells and microbial cells are shed from the skin

New microbial cells are produced and move towards the surface

New skin cells are produced and move towards the surface



Our skin flora lives both on and in the skin

This implies:

Disruptions at the surface are 'dealt with and repaired' from the inside-out.

This underlines:

Successful epidermal differentiation leads to a healthy skin flora

Cosmetic approaches



Cosmetics, desired approach



- A. $t=0$ Analysis of skin microflora on normal/aged/sensitive etc. skin
- B. Application of test products for x time
- C. $t=0+x$ Analysis of skin microflora. Improvements?

Note: Implies knowledge about what needs to be improved

In the search of cosmetic relevance

Understand the role of the skin microflora in, e.g.

- Sensitive skin (50% of people perceive their skin to be sensitive)
- Baby skin (e.g. diaper area)
- Aged skin (a growing demographic)
- Aging processes. Is there a relevant link with UV, pollution etc.?
(by far most 'anti-aging' cosmetics users are in their 30s)
- Oily skin (acne)
- Scalp (dandruff, irritation)
- Etc.



'Improve'

1. Identification of differences in microbial composition between benchmark skin (e.g. 'young', 'healthy') and e.g. 'aged skin', 'sensitive skin'.

Note 1: different locations on body, different composition

Note 2: reduced sebum production with aging in face does not necessarily mean that the microflora in the aged face plays a causative role in skin aging

2. Identification of role these differences play

e.g. Amway: specific corynebacteria live only on aged skin and others only on young skin. Do not co-exist. Corynebacteria on elderly skin said to be associated with skin redness (blotchiness).

3. Define ways how to influence the microbial composition
4. Active interference with skin microflora (directly or through skin)



'Balance'

1. Identification of healthy/'balanced' skin microflora
2. Help to preserve/quickly recover 'balance'

Top 10 bacterial species for different environments, i.e. balanced (?)

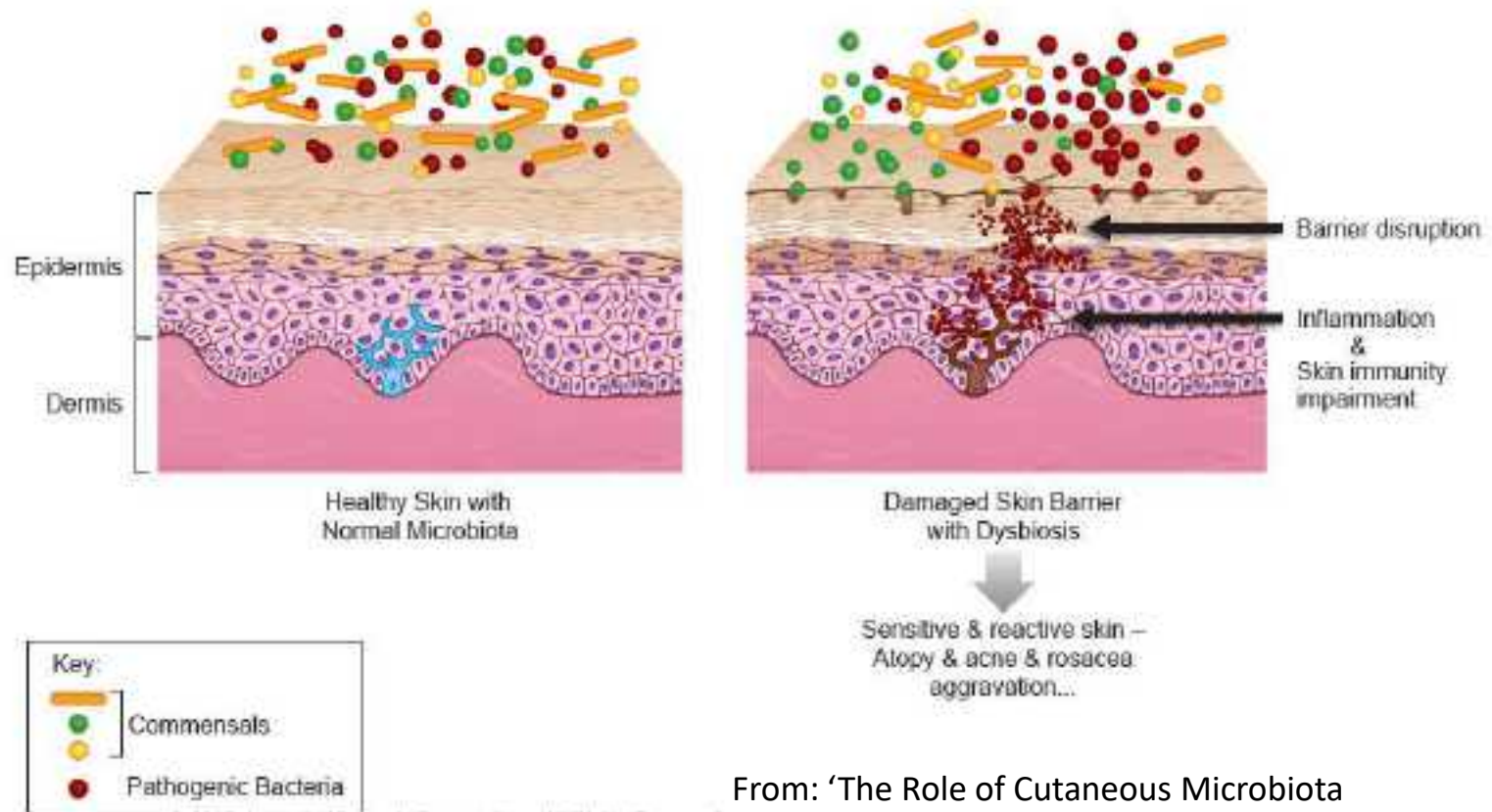
Dry*	Moist†	Sebaceous‡	Foot§
Bacteria			
<i>Propionibacterium acnes</i>	<i>Corynebacterium tuberculo</i> stearicum	<i>Propionibacterium acnes</i>	<i>Corynebacterium tuberculo</i> stearicum
<i>Corynebacterium tuberculo</i> stearicum	<i>Staphylococcus hominis</i>	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus hominis</i>
<i>Streptococcus mitis</i>	<i>Propionibacterium acnes</i>	<i>Corynebacterium tuberculo</i> stearicum	<i>Staphylococcus warneri</i>
<i>Streptococcus oralis</i>	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus capitis</i>	<i>Staphylococcus epidermidis</i>
<i>Streptococcus pseudopneumoniae</i>	<i>Staphylococcus capitis</i>	<i>Corynebacterium simulans</i>	<i>Staphylococcus capitis</i>
<i>Streptococcus sanguinis</i>	<i>Corynebacterium fastidiosum</i>	<i>Streptococcus mitis</i>	<i>Staphylococcus haemolyticus</i>
<i>Micrococcus luteus</i>	<i>Corynebacterium a</i> fermentans	<i>Staphylococcus hominis</i>	<i>Micrococcus luteus</i>
<i>Staphylococcus epidermidis</i>	<i>Micrococcus luteus</i>	<i>Corynebacterium aurimucosum</i>	<i>Corynebacterium a</i> fermentans
<i>Staphylococcus capitis</i>	<i>Enhydrobacter aerosaccus</i>	<i>Corynebacterium kroppenstedtii</i>	<i>Corynebacterium simulans</i>
<i>Veillonella parvula</i>	<i>Corynebacterium simulans</i>	<i>Corynebacterium amycolatum</i>	<i>Corynebacterium resistsens</i>

From: 'The human skin microbiome', Byrd AL et al, Nat Rev Microbiol 2018 Mar;16(3):143-155.



Compensate for a dysbiosis

A dysbiosis of the skin microflora can have negative implications:
compensate for this



From: 'The Role of Cutaneous Microbiota Harmony in Maintaining a Functional Skin Barrier', Baldwin HE et al, J Drugs Dermatol. 2017 Jan 1;16(1):12-18



Conclusions

- Probiotic lysates are established cosmetic ingredients
- The skin microflora extensively interacts with the skin with many important outcomes
- The activity of probiotic lysates shows strong overlap with the activity of the 'healthy' skin microflora
- Cosmetically influencing the skin microflora means understanding its role in cosmetically relevant topics
- It is a young science, but we are gathering more info on human-microbial interaction every day!

