A Natural Solution with Skin Microbiome Friendly Multifunctional Activities

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Abstract

The generation of odour on various sites of the human body, is mainly caused by microbial transformation of odourless natural skin secretions into volatile odorous molecules. Volatile fatty acids (VFAs such as 3M2H and HMHA), along with thioalcohols and 16-androstene steroids, are causal molecules synthesised by skin bacteria of axillary malodour.

Several tests are carried out to evaluate *Zanthoxylum bungeanum* fruit extract (ZBFE): astringency, *Corynebacterium xerosis* lipase inhibitory test, bacterial cytotoxicity is evaluated on *Staphylococcus epidermis ATCC* 12228 and *Corynebacterium xerosis* ATCC 373. A sniff test on axillary areas of human volunteers is carried on over an 8^H journey against a placebo.

ZBFE shows a +295% more astringent capacity than tannic red wine. It has no inhibitory properties on *S.epidermidis* and *C.xerosis* growth at normal usage level. At 3% it inhibits by -181% lipase from *C.xerosis* decreasing triglycerides hydrolysis into odoriferous compounds. Clinical expert self-evaluation of armpit odour after a single application of a roll-on formulation containing 3% ZBFE shows a decrease of -57,1% of the odour after 8^H compared to the placebo.

ZBFE is a full body care product with a microbiota friendly action through inhibition of bacterial enzymes that generate odoriferous compounds and with astringent, protective, hydrating, and antioxidant properties.

Keywords: Zanthoxylum bungeanum, microbiota, deodorant, lipase, Corynebacterium xerosis

Introduction

In the quest for mental and physical well-being, it is essential today for consumers to accept their appearance, learn to love their body by taking care of it as a whole: to be “body positive”. A new wave of holistic, honest, and inclusive products is coming to market to challenge the dictates of society. It is time to upgrade our daily body care routine and treat it with high-quality, high-performance, microbiome-friendly ingredients typically reserved for the face. Products with anti-acne, odour neutraliser, soothing, moisturising and even anti-ageing claims have their place in this approach.

Human scent is genetically controlled and systemically influenced by gender and ethnicity, along with emotional, physiological, and environmental factors (influence of the composition and quantity of sweat). Body malodour, including foot odour, suppresses social interaction by diminishing self-confidence (1).

According to the IFSCC monograph on underarm technology, individuals have been trying to control body odour for at least 3 500 years. The earliest methods are attributed to the Chinese, who mixed aromatic gums with fats to form an ointment to mask odours on various body areas. Today over 90% of the US population uses some form of antiperspirant or deodorant daily (2).

Eccrine sweat glands are of critical importance for the regulation of body temperature. Apocrine glands are larger sweat glands, restricted to hirsute areas, predominantly in the axillae, perineal region, and scalp. They do not contribute to thermoregulation, but rather serve as scent glands (3). Within the axilla, apocrine glands outnumber eccrine by 10 to 1 (1).

Axillae is an area where bacterial density is the highest ($2.4x10^6$/cm²). Indeed, this is a hot and humid zone, rich in growth factors. Most skin bacteria are Gram positive: Micrococcaceae, mainly *Staphylococcus* species ($10^{4.4}$/cm²) (60% are *S. epidermidis)*, aerobic Coryneforms, primarily *Corynebacterium* species ($10^{4.7}$-$10^{5.8}$/cm²), and anaerobic/microaerophilic *Propionibacterium* species (4).

Corynebacterium xerosis and *Staphylococcus epidermidis* are well known commensal bacteria. *S. epidermidis* is considered a probiotic strain because of its ability to prevent colonisation of more pathogenic bacteria (5).

Gram-negative bacteria give nearly no contribution to the axillary malodour. *Corynebacteria* gram positive, generates intensive and pungent malodours, while high numbers of *Staphylococci* correlate with a "faint acid, nonapocrine" odour quality (6) (7) (8) (9) (10).

The generation of odour on various sites of the human body, *e.g.* foot, mouth, or axilla, is mainly caused by microbial transformation of odourless natural skin secretions into volatile odorous molecules (8). A consensus has emerged that short (C_2–C_5) and medium-chain (C_6–C_{12}) VFAs (such as 3M2H and HMHA), along with thioalcohols and 16-androstene steroids, are causal molecules of axillary malodour (7) (8) (11).

Zanthoxylum plants are known as 'toothache trees' due to the analgesic properties of their bark and fruit. Major ethnobotanical properties attributed to this plant species are relief of dental problems, gastrointestinal disorders, effective for rheumatism, analgesic, and action against various skin diseases. *Zanthoxylum*'s berry is commonly used in Japan as a spice (12).

Zanthoxylum bungeanum fruit extract (ZBFE) is evaluated for its global body care actions with multifunctional properties particularly for its malodour control and skin microbiota friendly capacity.

Several tests are carried out to evaluate ZBFE: astringency, *Corynebacterium xerosis* lipase inhibitory test, bacterial cytotoxicity is evaluated on *Staphylococcus epidermis* and *Corynebacterium xerosis*. And finally, a Sniff test on axillary areas of human volunteers is carried on over an 8^H journey against placebo.

Materials

Astringency

The *in tubo* assay for determining a product's astringency capacity is based upon tannin-polymer interaction resulting in the formation of insoluble polymer tannin complexes which then precipitates. The difference in optical density (OD) before and after precipitation corresponds to the astringency capacity of the product.

Samples are incubated with and without Methylcellulose and the OD at 280nm is measured by spectrophotometer. The precipitated part of the extract corresponds to the astringent tannin fraction. The OD of epicatechin at increasing concentrations establishes a calibration curve.

Minimal Inhibitor Concentration - MIC

Each concentration point diluted in the culture medium is inoculated by microbial strain at 5.10^5 cfu/ml for *Staphylococcus epidermis* (ATCC 12228), and $2.5.10^5$ cfu/ml for *Corynebacterium xerosis* (ATCC 373) per well (96 well plate / cfu: Colony Forming Unit). Then the assay is incubated 48^H at 32.5°C ±2.5°C, taking care of the respiratory type of the tested strain.

After the incubation time, the presence or absence of a trouble reveals a microbial growth. The last concentration corresponds to the lack of microbial growth and is selected as MIC for the tested strain.

Inhibition of Lipase from Corynebacterium xerosis

Hydrosoluble lipases can hydrolyse triglycerides into glycerol and free fatty acids. Liposoluble glyceryl tributyrate used as a substrate is hydrolysed in glycerol and hydrosoluble butyric acid. The trouble of the culture medium will disappear proportionally with the hydrolysis of the glyceryl tributyrate. This trouble is measured at 620nm by spectrophotometry.

Two methods have been used to demonstrate the anti-lipase activity of ZBFE: one method in liquid medium and one method on agar plate.

Antioxidant Capacity

DPPH:
The oxydo-reduction decolourisation of the violet DPPH to yellow DPPH-H is followed by a spectrophotometry with and without ZBFE.

O_2 Singlet:
A system generating O_2 singlet is receiving ZBFE. The degradation of Uric acid is followed by spectrophotometry.

Soothing Effect

Normal Human Dermal Fibroblasts (NHDF) are incubated with the test product for 24^H. They are then irradiated or not with UVB at 60mJ/cm² and re-incubated with the product for another 24^H. PGE_2 and IL6 synthesised is quantified in the supernatant of the cell culture by ELISA.

Hydrating Effect

Hyaluronic Acid:
Human Epidermal Keratinocytes (HaCaT) are cultivated on 24 well plates. They are incubated for three days with and without the test product at different concentrations. Hyaluronic acid synthesis is quantified by ELISA.

Keratinocyte Pro-Differentiating Effect:
Normal Human Epidermal Keratinocytes (NHEK) differentiation is followed up visually for 4 days by phenotype observation in the presence or absence of ZBFE.

Sniff Test

The underarm odour intensity is self-evaluated from T0 to 8 hours after application (T8) of a roll-on formulation containing 3.0% ZBFE versus placebo. The trial takes place over three days: one day for odour wash out, one day with the placebo on one side and the active roll-on on the other side, and the opposite on the following day. Volunteers are asked to not eat spicy food, onions, or garlic starting from day one, and not to use any perfumed products. Scores from 5 very good odour to 0 none are attributed every hour. 14 volunteers are recruited, with two evaluations per volunteer, which makes it to a total of 28 sets of data.

Measurement data is automatically computerised and after a validity check and quality assurance, stored centrally in a database. First the normality of values is determined by a Normality check on each set of difference data with a Shapiro-Wilk test. Statistical calculation is then performed using a two-sided unpaired Student t test for non-parametric values or a Mann Whitney test of ranks.

The 0.05 level is selected as the point of minimal acceptance of statistical significance.

Results:

Astringency
The word astringency, from the Latin *ad stringem,* meaning ‘to bind’, reflects what is believed to be the primary chemical process that gives rise to the sensation. Compounds that can bind with and cross-link proteins are astringents (13).

So far, a majority of publications consider astringency as a tactile sensation that can occur on skin, hair, mucosa, and is described by four terms: astringency, dryness, pucker, ‘roughing’ (i.e., roughness) (14) (15). Astringency often also causes sensations of tightness and constriction.

An astringent substance, able to shrink or constrict body tissues by aggregation, would be perfectly adapted to:
- Constrict enlarged pores and reduce excessive oiliness and sweat secretion,
- Remove sebum excess (16).

The following table presents Methyl Cellulose Precipitation (MCP) results:

		Mean MCP Tannin (% eq epicatechin)	Standard Deviation	% Variation vs Tannic wine
Tannic Wine	n=4	1 334	222	*Reference*
ZBFE	n=12	5 276	161	**295%***
Tannic Acid	n=4	3 326 242	296 369	

Table 1: MCP Quantification. A Brown Forsythe and Welch Anova test of the control + vs ZBFE for parametric values with heterogeneous variance has been processed. *p<0.0001.

ZBFE shows a statistically higher astringent capacity of 295%* compared to tannic red wine positive control.

Minimal Inhibitor Concentration - MIC

	MIC
ZBFE	
C.xerosis	14%
S.epidermidis	>20%
Benchmark 1	
S.epidermidis	0.01%
Benchmark 2	
C.xerosis	0.63%
S.epidermidis	0.63%

Table 2: MIC Determination – ZBFE compared to two benchmarks.

Two benchmarks, widely used in deodorant product as antimicrobial agent, show a very low MIC with a value of 0.013% and 0.63% on *S.epidermidis* and *C.xerosis.*
ZBFE shows no antimicrobial properties (14% is considered to be too high as we advise to use the product at 3%) on *C.xerosis* nor on *S.epidermidis.* ZBFE can be considered as a microbiome friendly product as it does not alter microbial growth of two of the most important strains of the axillary region.

Inhibition of Lipase from Corynebacterium xerosis

	Negative Control		ZBFE		
	Relative Lipase Activity	Standard Deviation	Relative Lipase Activity	Standard Deviation	% Variation ZBFE vs Negative Control
0^H	100.00	0.00	100.00	0.00	0,00
48^H	41.67	0.06	62.36	1.13	-49.7%*
72^H	23.17	0.20	65.12	0.18	-181.1%*

Table 3: Lipase Relative Activity. An Anova test of the control - vs ZBFE for parametric values with homogeneous variance has been processed. *p<0.0001. ns: not statistically different.

The generation of free fatty acids from skin lipids, catalysed by secreted lipases, is the first step in the biotransformation of long chain fatty acids (LCFAs). *Propionibacteria* and aerobic coryneforms have been particularly shown to exhibit strong lipase activity (17).

The highly active lipase of *Corynebacteria* plays a pivotal role in the formation of malodorous short-medium chain (C_2–C_{11}) VFAs in the axilla.

ZBFE at 3% decreases statistically significantly by 181% the lipase activity of *C.xerosis* at 72^H.

Antioxidant Capacity

Oxidative stress plays a central role in the cutaneous response to various stresses. Free radicals (H_2O_2, OH•, O_2^-, O_2, $^1O_2$ …) lead to protein, lipid, and DNA damages, undergoing cell damage and ultimately cell death.

DPPH assay

Product	Conc	Mean ROS (Corrected DO)	Standard Deviation	Decrease in ROS (%)
CTRL	-	0.268	0.005	Ref
ZBFE (N=1, n=6)	2%	0.109	0.048	-59%*
	3%	0.101	0.037	-62%*

Table 4: *In Tubo* DPPH Measurement. Results are the average of six values (n=6). Bilateral student t test for parametric unpaired values with homogenous variances. *p<0.01.

ZBFE decreases statistically significantly by -62%* ROS from DPPH at 3%, in the experimental condition of this assay. The effect is dose dependant. PG has no DPPH activity (data not presented).

O_2 Singlet assay

		N=1			N=2			Total Mean ROS (ΔDO_{292})
Product	Conc	Mean ROS (ΔDO_{292})	Standard Deviation	Decrease in ROS (%)	Mean ROS (ΔDO_{292})	Standard Deviation	Decrease in ROS (%)	
CTRL	-	33.82	1.72	Ref	32.33	0.81	Ref	Ref
ZBFE (N=2, n=2 or 3)	2%	23.95	0.37	-29%*	20.02	0.95	-38%*	-34%
	3%	19.25	1.94	-43%*	14.87	1.49	-54%*	-49%

Table 5: *In Tubo* O_2 Singlet Measurement. Experiment is proceeded twice (N=2). Results are the average of two to three values (n=2 or 3). Bilateral student t test for parametric unpaired values with homogenous variances. *p<0.01.

ZBFE decreases statistically significantly by -49% ROS from O_2 singlet at 3%, in the experimental condition of this assay. PG has no O_2 singlet reducing activity (data not presented).

Soothing Effect

PGE_2 plays an important role in inflammation and acts as a direct vasodilator by acting on smooth muscle to cause dilation of blood vessels as well as angiogenesis, and vascular permeability.
PGE_2 is responsible for redness, swelling and pain on inflammation site (18) and is highly increased after a single acute exposure to UV radiation (19) (20). Evidence shows that it mediates UV induced systemic immunosuppression (21).

IL-6 is involved in a lot of regulation processes. It plays a key role in chronic inflammation regulation as well as in age-related senescence. Hence, its synthesis and its action need to be modulated.

Product	Conc	Conditions	Cell Viability	Mean PGE_2 ($pg/10^6$ cell)	Standard Deviation	Variation (%)
CTRL	-	NI	Ref	1740	33	Ref
ZBFE (n=3)	2%		-1%	412	20	-76%*
CTRL	-		Ref	1613	49	Ref
ZBFE (n=3)	3%		-1%	334	35	-79%*
CTRL	-	UVB	Ref	8700	750	Ref
ZBFE (n=3)	2%		-7%	2789	349	-68%*
CTRL	-		Ref	8539	683	Ref
ZBFE (n=3)	3%		-7%	1053	208	-88%*

Product	Conc	Conditions	Cell Viability	Mean IL6 (pg/10^6 cell)	Standard Deviation	Variation (%)
CTRL	-	NI	Ref	1374	26	Ref
ZBFE (n=3)	2%		-1%	892412	25	-35%*
CTRL	-		Ref	1244	32	Ref
ZBFE (n=3)	3%		-1%	627	54	-50%*
CTRL	-	UVB	Ref	10058	922	Ref
ZBFE (n=3)	2%		-7%	6188	296	-38%*
CTRL	-		Ref	9238	323	Ref
ZBFE (n=3)	3%		-7%	3399	181	-63%*

Table 6: PGE_2 & IL6 Quantification with ZBFE ON NHDF irradiated or not by UVB. Results are the average of three values (n=3). Bilateral student t test for parametric unpaired values with homogenous variances. *p<0.01. NI: Not Irradiated. Cell viability is measured by Hoechst coloration.

ZBFE at 3% decreases statistically significantly by -89%* PGE_2 and by -63%* IL6 synthesis after UVB irradiation. It also decreases statistically significantly PGE_2 and IL6 in homeostasis condition by -79%* and -50%* respectively.

Hydrating Effect

Hyaluronic Acid

The *stratum corneum* (SC) plays a very important role against dry stress. Accordingly, moisturisation of the SC is highly important for maintaining its flexibility and desquamation (22). Water content of skin is remarkably high in viable epidermis (more than 70%), and sharply drops at the junction between the *stratum granulosum* (SG) and SC to 15-30% water (23).

If SC water content falls below a critical level, enzymatic function required for normal desquamation is impaired, leading to corneocyte adhesion and accumulation on the cutaneous surface, and the visible appearance of dryness, roughness, scaling, flaking and even a dull complexion (23).

Natural Moisturising Factor (NMF) and lipids play an important role in moisturisation. Hyaluronic Acid (HA) is also well known to be a water absorbed macromolecule (HA can bind 1000 times its weight in water). HA is reported to have not only hydrophilic but also a hydrophobic properties. Indeed, HA interacts with phospholipids of the lamella structure in the SC that might serve to regulate mechanical properties of the SC (22).

Skin contains in the dermis 0.20 – 0.50 mg/g and 0.10 mg/g in the epidermis, or about 50% of the total HA in a given organism (22).

Product	Conc	Cell viability	Mean Extracellular Synthesis of Hyaluronic Acid (ng/10^6 cell)	Standard Deviation	Variation (%)	Total Mean HA (ng/10^6 cell)
CTRL	-	Ref			Ref	Ref
ZBFE (n=5)	0,14%	0%	484	77	45%*	49%
		-15%	517	39	52%*	
	0,26%	-7%	867	98	159%*	208%
		-21%	1215	106	257%*	

Table 7: Hyaluronic Acid Quantification. Results are the average of ten values (n=5, N=2). Bilateral student t test for parametric unpaired values with homogenous variances. *p<0.01. Cell viability is measured by Hoechst coloration.

ZBFE increases statistically significantly by +208%* Hyaluronic Acid synthesis at 0,26%.

Keratinocyte Pro-Differentiating Effect

SC is a semipermeable protective layer that prevents ~~from~~ water loss and maintains skin hydration. During the differentiation process, keratinocytes permanently withdraw from the cell cycle, initiate expression of epidermal differentiation markers like keratins, involucrin, loricrin, transglutaminase, filaggrin, and move suprabasally as they become part of corneocytes.

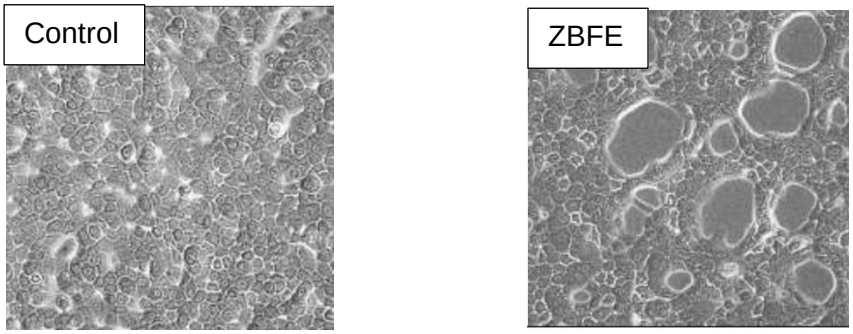

Table 8: Pro Differentiating Effect of ZBFE. Results are the average of six values (n=3, N=2).

ZBFE increases the differentiation in keratinocyte resulting in an improved protection of the epidermis and ~~a~~ better moisturisation.

Sniff Test

Below is described the results from the evaluation of body malodour of volunteers over eight hours.

Whole Panel of Volunteers									
Time (h)		1	2	3	4	5	6	7	8
Placebo	Mean	4.7	4.3	3.9	3.3	3.0	2.6	2.1	1.7
	Standard Deviation	0.55	0.65	0.71	0.55	0.47	0.57	0.63	0.71
ZBFE 3% Cream	Mean	4.9	4.8	4.4	4.0	3.6	3.3	2.7	2.3
	Standard Deviation	0.31	0.42	0.62	0.61	0.69	0.81	0.78	0.94
Variation vs placebo (%)		4.6%	12.6%*	13.0%*	20.4%*	20.2%*	27.8%*	29.7%*	35.4%*
Expert Panel									
Placebo	Mean	4.5	4.0	3.6	3.4	3.1	3.0	2.5	2.1
	Standard Deviation	0.53	0,82	0,52	0,52	0.32	0.00	0.53	0.74
ZBFE 3% Cream	Mean	5.0	4.8	4.7	4.2	4.0	3.8	3.5	3.3
	Standard Deviation	0.00	0.63	0.67	0.63	0.47	0.42	0.50	0.48
Variation vs placebo (%)		11.1%*	20.0%*	30.6%*	23.5%*	29.0%*	26.7%*	38.0%*	57.1%*

Table 9: Odour Self-Assessment Score. Bilateral student t test for non-parametric unpaired values or a Mann Whitney test of ranks. *p≤0.01.

ZBFE's cream statistically significantly decreases armpit malodour after 8 hours by 35%*.

Among the panellists from this trial, five experts participated in the trial. They are trained and used to odour and perfume~~s~~ evaluation. Expert evaluation of ZBFE's cream, shows a statistically significant decrease of armpit malodour after eight hours by 57.1%*.

Discussion and Conclusion

It is now generally accepted that skin bacteria cause body odour by biotransformation of sweat components secreted in the human axillae (8).

Currently it is believed that the benefits of healthy skin microflora are comparable with those of healthy gut flora. Studies support an emerging interactive relationship between the skin microbiota and cutaneous immunity. Low diversity has also been associated with some dysbiotic skin disorders (24) (25). Therefore, preserving it, seems increasingly important.

There is therefore a significant shift from the current reliance of deodorants on fragrances and broad-spectrum antimicrobial agents. A new generation of deodorant systems appears based on targeting specific bacteria, metabolic pathways, or key enzymes (7) (9).
Zanthoxylum bungeanum fruit extract (ZBFE) responds to this demand being a full body care product with a microbiota friendly action through inhibition of bacterial enzyme that generate odoriferous compounds and with astringent, protective, hydrating, and antioxidant properties.

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Conflict of Interest Statement
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Literature

1. Kanlayavattanakul M, Lourith N. Body malodours and their topical treatment agents. *International Journal of Cosmetic Science.* 2011, Vol. 33, pp. 298–311.
2. Abrutyn E, Wild J. Antiperspirant and deodorants: principles of underarm technology. *IFSCC Monograph N°6.* Weymouth, Dorset, England : Micelle Press, 1998.
3. Stoddart, DM. *The Scented Ape: The Biology and Culture of Human Odour.* s.l. : New York: Cambridge University Press, 1990.
4. Gueniche, A. *La sueur, la microflore et la biochimie de l'odeur des aisselles.* [ed.] Marek Haftek. Lyon : MatriX, 2017. ISSN 2266-9949.
5. Otto, M. Staphylococcus epidermidis – the "accidental" pathogen. *Nat Rev Microbiol.* 2009, Vol. 7, 8, pp. 555–567.
6. Troccaz M, Starkenmann C, Niclass Y, Van de Waal M, Clark AJ. 3-Methyl-3- sulfanylhexan-1-ol as a Major Descriptor for the Human Axilla-Sweat Odor Profile. *Chem. Biodiv.* 2004, Vol. 1, pp. 1022-1035.
7. James AG, Austin CJ,Cox DS, Taylor D and Calvert R. Microbiological and biochemical origins of human axillary Odour. *FEMS Microbiol Ecol.* 2013, Vol. 83, pp. 527–540.
8. Barzantny H, Brune I, Tauc A. Molecular basis of human body odour formation: insights deduced from corynebacterial genome sequences. *International Journal of Cosmetic Science.* 2012, Vol. 34, pp. 2-11.
9. Troccaz M, Borchard G, Vuilleumier C, Raviot-Derrien S, Niclass Y, Beccucci S, Starkenmann C. Gender-specific differences between the concentrations of non-volatile (R)/(S)-3-methyl-3-sulfanylhexan-1-ol and (R)/(S)-3-hydroxy-3-methyl-hexanoic acid odor precursors in axillary secretions. *Chem senses.* 2009, Vol. 34, pp. 203-210.
10. Laden, K. *Antiperspirants and deodorants.* 2nd edition. 1999.
11. James AG, Hyliands D and Johnston H. Generation of volatile fatty acids by axillary bacteria. *International Journal of Cosmetic Science.* 2004, Vol. 26, pp. 149–156.
12. Zhang M, Wang J, Zhu L, Li T, Jiang W, Zhou J, Peng W and Wu C. Zanthoxylum bungeanum Maxim. (Rutaceae): A Systematic Review of Its Traditional Uses, Botany, Phytochemistry, Pharmacology, Pharmacokinetics, and Toxicology. *Int. J. Mol. Sci.* 2017, Vol. 18, 2172.
13. Bate-Smith, EC. Haemanalysis of tannins: The concept of relative astringency. *Phytochemistry.* 1973, Vol. 12, pp. 907-912.
14. Lee CB, Lawless HT. Time-course of astringent sensations. *Chemical Senses.* 1991, Vol. 16, pp. 225-238.
15. Bajec MR, Pickering GJ. Astringency: Mechanisms and Perception. *Critical Reviews in Food Science and Nutrition.* 2008, Vol. 48, 8, pp. 1–18.
16. Reisner, RM. Acne vulgaris. *Pediatr Clin North Am.* 1973, Vol. 20, 4, pp. 851-64.
17. Troccaz, MC. *The biosynthetic pathway of sulfur-containing molecules in Human Axillary Malodor: from precursors to odorous volatiles.* Univ. Genève : Thèse de doctorat no. Sc. 4102, 2009.
18. Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. *Arterioscler Thromb Vasc Biol.* 2011, Vol. 31, 5, pp. 986–1000.
19. Rhodes LE, Gledhill K, Masoodi M, Haylett AK, Brownrigg M, Thody AJ, Tobin DJ, Nicolaou A. The sunburn response in human skin is characterized by sequential eicosanoid profiles that may mediate its early and late phases. *FASEB J.* 2009, Vol. 23, pp. 3947-3956.
20. Rundhaug JE, Fischer SM. Cyclo-oxygenase-2 Plays a Critical Role in UV-induced Skin Carcinogenesis. *Photochemistry and Photobiology.* 2008, Vol. 84, pp. 322–329.
21. Soontrapa K, Honda T, Sakata D, Yao C, Hirata T, Hori S, Matsuoka T, Ki Y. Prostaglandin E2–prostoglandin E receptor subtype 4 (EP4) signaling mediates UV irradiation-induced systemic immunosuppression. *PNAS.* 2011, Vol. 108, 16, pp. 6668–6673.
22. Sakai S, Yasuda R, Sayo T, Ishikawa O, Inoue S. Hyaluronan exists in the normal Stratum corneum. *J Invest Dermatol.* 2000, Vol. 114, 6, pp. 1184-7.
23. Bonté, F. Skin moisturization mechanisms: New data. *Annales Pharmaceutiques Françaises.* 2011, Vol. 69, pp. 135-141.

24. Grice, EA. The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease. *Semin Cutan Med Surg.* 2014 Jun, Vol. 33, 2, pp. 98–103.
25. Scharschmidt, TC. Establishing Tolerance to Commensal Skin Bacteria. *Dermatol Clin.* 2017 Jan, Vol. 35, 1.