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USE OF COMPOUNDS OF RETINOID TYPE AS ANTIBACTERIAL AGENTS

The invention relates to the use of at least one compound chosen from molecules of retinoid type for the preparation of a composition for preventively or curatively treating bacterial colonizations, aggravations of pathologies caused by these colonizations and also cutaneous overinfections induced by these bacteria and more particularly by the bacterium *Staphylococcus aureus*.

The invention also relates to the use of at least one compound chosen from molecules of retinoid type in a skin cleansing composition, and also to a cosmetic treatment method for cleansing the skin or correcting its odor, comprising the application of this composition to the skin.

Compounds of retinoid type are compounds with a biological activity profile similar to that of *all-trans*-retinoic acid or 9-*cis*-retinoic acid. These compounds can modify the expression of genes by means of receptors of the retinoic acid family, such as the RARs and RXRs. Thus, retinoids may show activity in the test of differentiation of mouse embryonic teratocarcinoma cells (F9) (Cancer Research 43, p. 5268, 1983) and/or in the test of inhibition of ornithine decarboxylase after induction with TPA in mice (Cancer Research 38, p. 793-801, 1978). These

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tests show the activities of these compounds in the fields of cell differentiation and cell proliferation, respectively.

These retinoids have already been described in many pharmaceutical applications, more particularly dermatological or cosmetic applications. In the pharmaceutical field, they have especially been proposed to treat dermatological, rheumatic, respiratory, cardiovascular and ophthalmological complaints. In the dermatological or cosmetic field, EP 0 379 367 especially discloses a method for preventively or curatively treating aged skin using retinoids.

Moreover, it is well known that the skin is covered with a flora that is responsible for a whole range of unpleasant effects ranging from the simple production of odor to more or less severe pathologies such as, for example, acne and/or dandruff.

Commensal microorganisms living on or in the skin may form part of a microflora that is either resident (normal) or transient. The resident organisms develop normally on or in the skin. Their presence is established in well-defined distribution profiles. The microorganisms that are temporarily present are referred to as transient. These microorganisms do not usually become permanently attached; they are incapable of multiplying and normally die after a few hours.

The anatomy and physiology of the skin vary from one part of the body to another and the resident microflora reflects these variations.

Most of the skin bacteria are present on the superficial squamous epidermis, colonizing the dead cells or closely associated with the sebaceous and sweat glands. Excretions from these glands provide water, amino acids, urea, electrolytes and specific fatty acids that serve as nutrient elements mainly for *Staphylococcus epidermidis* and aerobic corynebacteria.

Gram-negative bacteria are generally present in the more humid regions. Certain pathogenic agents present on or in the skin are resident/transient and colonize the areas around orifices. *Staphylococcus aureus* is the best example. It is resident in the nostrils and the perianal region, but transient on the other parts of the body, where it has difficulty in surviving.

Theoretically, the epidermis is an unfavorable environment for colonization by microorganisms. Several factors, for instance periodic drying of the skin, the slightly acidic pH of the skin, the high concentration of sodium chloride in the sweat, and certain natural inhibitory substances (bactericides and/or bacteriostatic agents), are responsible for this hostile microenvironment.

The acidic pH (4-6) of the skin, due to the

organic acids produced by the staphylococci and to the secretions from the sebaceous and sweat glands, discourages colonization by many microorganisms.

Sweat contains sodium chloride in a concentration that establishes hyperosmotic conditions at the surface of the skin and is an osmotic burden on many microorganisms.

Finally, certain natural inhibitory substances help in controlling colonization, excessive growth and infection of the surface of the skin by the resident microorganisms. For example, the sweat glands excrete lysozyme which lyses *Staphylococcus epidermidis* and other Gram-positive bacteria.

Certain gram-positive bacteria (*Propionibacterium acnes*) can change the lipids secreted by the sebaceous glands into unsaturated fatty acids, such as, for example, oleic acid, which show strong antimicrobial activity on Gram-negative bacteria and mycetes.

However, under certain conditions, this natural defense system can, although being effective, show unpleasant effects, or may even be caught out.

For example, certain natural inhibitory substances (bactericides and/or bacteriostatic agents) due to the partial degradation of complex lipids secreted by the sweat glands are volatile and may be associated with a strong odor that it is customary to

combat. Admittedly, many deodorants contain antibacterial substances that act selectively on the Gram-positive bacteria responsible for these degradations to reduce the production of aromatic unsaturated fatty acids and body odor. However, the deodorants can modify the microflora, mainly toward the Gram-negative bacteria, and consequently trigger infections.

It thus remains advantageous to have available, in the context of treating body odor, effective compounds and/or compositions that have no side effects.

Another example is *Propionibacterium acnes*, the bacterium most commonly associated with the cutaneous glands, which is an anaerobic and lipophilic Gram-positive rod. This bacterium is usually harmless. However, it has been associated with a skin disease: juvenile acne. Acne ordinarily appears during adolescence when the endocrine system is very active. The hormonal activity stimulates the overproduction of sebum, a fluid secreted by the sebaceous glands. A large volume of sebum accumulates in the glands and provides a microenvironment that is ideal for *Propionibacterium acnes*. In certain individuals, this accumulation triggers an inflammatory response causing redness and swelling of the glandular duct and producing a comedone, which is a plug of sebum and

keratin in the canal. This results in inflammatory lesions (papules, pustules and nodules), commonly known as "blackheads". *Propionibacterium acnes* appears to be the organism that produces lipases which degrade the triglycerides of the sebum into free fatty acids. These derivatives are particularly irritant since they can penetrate into the dermis and give rise to inflammation.

Strains of *Staphylococcus aureus* are known to produce toxins and superantigens, which promotes the appearance of irritation reactions and of inflammatory processes. Thus, more than 90% of cases of atopic dermatitis present this bacterium (British Journal of Dermatology, 1998: 139: 13-16).

Moreover, it has been demonstrated that patients suffering from atopic dermatitis can act as reservoirs for the transmission of *Staphylococcus aureus* to other individuals. The studies presented in Pediatric Dermatology, vol. 15, No. 3, 194-198, 1998 suggest that the nostrils and the hands are, respectively, major reservoirs and vectors for transmission of this bacterium to damaged skin and individuals in close contact with these patients.

It is thus important to treat these individuals suffering from atopic dermatitis, in order to prevent the aggravation of the pathology from which they are suffering, and in particular to prevent the

risk of massive overinfection with *Staphylococcus aureus*, as is the case for "scalded skin syndrome", but also to take preventive measures with regard to individuals who come into contact with these patients and who are liable to develop bacterial infections, in particular in a hospital environment (International Journal of Dermatology, November 1986, vol. 25, No. 9).

An article published on pages 520 to 532 of the review entitled "The New England Journal of Medicine", vol. 339, No. 8 shows the current state of knowledge regarding the bacterium *Staphylococcus aureus*, its epidemiology and the treatment of diseases in which this bacterium is involved. It emerges from this document that the levels of colonization are thought to be higher among patients suffering from type 1 diabetes, intravenous-route drug users, blood dialysis patients, patients who have undergone surgery and patients carrying the human immunodeficiency syndrome. Individuals with qualitative or quantitative leukocyte defects are also thought to form part of an at-risk population with regard to colonization by the bacterium *Staphylococcus aureus*.

Obviously, it has been known practice for a long time to use, if necessary, compounds such as antibiotics.

However, in this case also, it is known that the use of such compounds presents appreciable negative

aspects. The abusive use of antibiotics may result in the emergence of resistant microorganisms on which they are no longer effective. Thus, in this case also, there is a need for effective compounds and/or compositions.

In this regard, FR 2 736 548 discloses the use of a retinoid for the preparation of a bacterial medicinal product. However, the retinoids used are aldehydes with weak antibacterial activity and which are, on account of their aldehyde function, cytotoxic and potentially allergizing.

Entirely surprisingly and unexpectedly, the Applicant has found that certain compounds of retinoid type have pronounced antibacterial activity and in particular pronounced antibacterial activity towards the bacterium *Staphylococcus aureus*.

This discovery forms the basis of the present invention.

The present invention thus relates to the use of at least one compound of retinoid type in an effective amount for the preparation of a composition for preventively or curatively treating bacterial colonizations, said compound being chosen from compounds 1 to 45 indicated in table 1 below.

	Table 1
No.	Chemical name
1	6-[3-(1-Adamantyl)-4-methoxy-5-hydroxyphenyl]-2-naphthoic acid
2	4-[4-(6-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
3	4-[4-(6-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
4	6-[2-Methyl-4-hydroxy-5-(1-adamantyl)phenyl]-2-naphthoic acid
5	4-[3-(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dienylidene)prop-1-ynyl]benzoic acid
6	2-Hydroxy-4-[4-(4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
7	2-[3-(1-Adamantyl)-4-methoxyphenyl)ethynyl]-4-thiophenecarboxylic acid
8	4-[4-(4,4'-Dimethylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
9	4-Hydroxy-2'(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid
10	2"-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid
11	6-(3-Adamantan-1-yl-5-bromo-4-hydroxyphenyl)-naphthalene-2-carboxylic acid

12	4-[4-(6,4'-Dimethylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
13	2'-(4,4-Dimethylthiochroman-6-yl)[1,1';4',1"]-terphenyl-4"-carboxylic acid
14	2'-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid
15	4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphtho-[2,3-b]thiophen-2-yl)benzoic acid
16	4-[(6-Hydroxy-7-(1-adamantyl)-2-naphthyl]benzoic acid
17	4-[2-Nonyloxyimino-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetylamino]benzoic acid
18	4-[3-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-phenylethynyl]-2-hydroxybenzoic acid
19	4-[[3-(1-Adamantyl)-4-[(2-methyl-3-hydroxypropyloxy)phenyl]ethynyl]]benzoic acid
20	2-Hydroxymethyl-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydroanthracen-2-yl)phenol
21	4-[4-(4'-Propylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
22	2-Hydroxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanylethynyl)benzoic acid
23	2'-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

24	6-[Butoxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]naphthalene-2-carboxylic acid
25	4-[3-(1,1-Dimethyldecyl)-4-methoxybenzoylamino]-benzoic acid
26	4-(3-Adamantan-1-yl-4-hexyloxybenzoylamino)benzoic acid
27	6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-napthylmethanol
28	2-Hydroxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydroanthracen-2-yl)benzoic acid
29	2-(3-Adamantan-1-yl-4-hydroxyphenyl)benzofuran-5-carboxylic acid
30	4-[6-Methoxyethoxymethoxy-7-(1-adamantyl)-2-naphthyl]salicylic acid
31	(E)-4-[4-(5-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
32	4-[4-(3-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
33	4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-naphthalen-2-ylselanylethynyl)benzoic acid
34	2-Methoxymethoxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1;4'1"]terphenyl-4"-carboxylic acid
35	2-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4'1"]terphenyl-4"-carboxylic acid

36	4-[(Z)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-undecenamido]benzoic acid
37	4-[4-(4'-Methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid
38	2'-Propoxy-5'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)biphenyl-4-carboxylic acid
39	4-[2-Heptyloxyimino-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetylamino]-benzoic acid
40	6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)naphthalene-2-carboxylic acid amide
41	(2-Dimethylaminoethyl)amide of 6-(3-adamantan-1-yl-4-methoxyphenyl)naphthalene-2-carboxylic acid
42	2-Hydroxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanylethynyl)benzoic acid
43	2'-(3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid
44	3-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid
45	3-(5'-Adamantan-1-yl-4'-methoxy-2'-methylbiphenyl-3-yl)acrylic acid

The bacterial colonizations that are particularly targeted by the present invention are colonizations by the bacterium *Staphylococcus aureus* and colonizations by the bacterium *Propionibacterium acnes*.

The present invention also relates to the use, in an effective amount, of at least one compound chosen from compounds 1 to 45 of Table I for the preparation of a composition for preventively or curatively treating aggravations of pathologies caused by a bacterial colonization.

Among the pathologies that may be aggravated by a colonization by the bacterium *Staphylococcus aureus*, mention may be made of impetigo or atopic dermatitis.

Among the pathologies that may be aggravated by a colonization by the bacterium *Propionibacterium acnes*, mention may be made of acne.

Certain compounds indicated in Table I and thus having pronounced antibacterial activity also show biological activity of RAR receptor antagonist type. This is the case in particular for the compounds indicated in the list below:

4-[4-(6-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(6-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[6-Methoxyethoxymethoxy-7-(1-adamantyl)-2-naphthyl]salicylic acid

(E)-4-[4-(5-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(3-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2-Methoxymethoxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1;4'1"]terphenyl-4"-carboxylic acid

4-[4-(4'-Methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(4'-Propylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid.

Now, it is known that RAR receptor antagonist compounds induce anti-inflammatory and immunomodulatory effects. Thus, in an animal model of chronic eczema, RAR receptor antagonist compounds have shown inhibitory effects on the clinical and histological signs of inflammation similar to those induced with glucocorticoids or immunomodulators of the macrolide family, for instance tacrolimus, without, however, causing the appearance of a side effect such as cutaneous atrophy, as is the case after a treatment with glucocorticoids (*A. Jomard et al., J. Invest. Dermatol. Vol. 110, No. 4, April 1998, page 577*).

Thus, the compounds that show pronounced antibacterial activity on *Staphylococcus aureus* and RAR

antagonist activity, as is the case for the compounds mentioned above, are particularly suitable for treating atopic dermatitis since they act simultaneously on two targets that are anomalies of the immune system and the proliferation of the bacterium *Staphylococcus aureus*.

Other compounds indicated in Table I and thus showing pronounced antibacterial activity also have biological activity of RAR receptor agonist type. This is the case in particular for the compounds indicated in the list below:

6-[3-(1-Adamantyl)-4-methoxy-5-hydroxyphenyl]-2-naphthoic acid

4-[3-(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dienylidene)prop-1-ynyl]benzoic acid

2-[3-(1-Adamantyl)-4-methoxyphenyl)ethynyl]-4-thiophenecarboxylic acid

4-Hydroxy-2'(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2"-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahyrdonaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

6-(3-Adamantan-1-yl-5-bromo-4-hydroxyphenyl)-naphthalene-2-carboxylic acid

2'-(4,4-Dimethylthiochroman-6-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2'-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-

tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphtho[2,3-b]thiophen-2-yl)benzoic acid

4-[(6-Hydroxy-7-(1-adamantyl)-2-naphthyl]benzoic acid

Now, it is known that RAR receptor agonist compounds modify the differentiation of keratinocytes (keratolytic effects) and of sebocytes (regression of the size of the sebaceous gland) and, by this means, can prevent the formation of comedones, which at least partly explains their beneficial effect in the treatment of acne.

Thus, the compounds that show pronounced antibacterial activity and RAR agonist activity, as is the case for the compounds mentioned above, are particularly suitable for treating acne since they act simultaneously on two targets that are anomalies of differentiation of eukaryotic cells (keratinocytes and sebocytes) which is the cause of the formation of comedones and the proliferation of the bacterium *Propionibacterium acnes*.

The present invention also relates to the use, in an effective amount, of at least one compound chosen from compounds 1 to 45 of table I for the preparation of a composition for preventively or curatively treating cutaneous overinfections induced by a bacterial colonization.

Among the cutaneous overinfections induced by a bacterial colonization by the bacterium *Staphylococcus aureus*, mention may be made of "scalded skin syndrome".

The pronounced antibacterial activity of the compounds of the present invention on the bacterium *Staphylococcus aureus* may be demonstrated by tests such as those described in the publication entitled "National committee for clinical laboratory standards" Vol. 13, No. 25, December 1993, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically-third edition, approved standard".

The bacterium *Staphylococcus aureus* CIP52.1 may be used in order to determine for each test compound the minimum inhibitory concentration for the bacterium, or MIC, expressed in μM.

In the present invention, the expression "compound with pronounced antibacterial activity on the bacterium *Staphylococcus aureus*" means any compound that shows in the antibacterial activity test indicated above a minimum inhibitory concentration for the bacterium of less than or equal to 5 μM. Preferably, the compound with pronounced antibacterial activity on the bacterium *Staphylococcus aureus* has a minimum inhibitory concentration for the bacterium of less than or equal to 2.5 μM and advantageously less than or equal to 2 μM.

The test results of the compounds according to the invention are given in example 1 of the present patent application.

The compounds according to the invention may be administered enterally, parenterally, topically or ocularly.

Via the enteral route, the pharmaceutical compositions may be in the form of tablets, gel capsules, coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres, nanospheres or lipid or polymer vesicles allowing a controlled release. Via the parenteral route, the compositions may be in the form of solutions or suspensions for infusion or for injection.

The compounds according to the invention are generally administered at a daily dose of about from 0.001 mg/kg to 500 mg/kg and preferably of about from 0.01 mg/kg to 50 mg/kg of body weight in 1 to 3 dosage intakes.

Via the topical route, the pharmaceutical compositions based on compounds according to the invention are intended for treating the skin and mucous membranes and are in the form of ointments, creams, milks, salves, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be in the form of lipid or polymer microspheres or nanospheres or vesicles or polymer patches and

hydrogels allowing a controlled release. These topical-route compositions may be in anhydrous form, in aqueous form or in the form of emulsions.

Via the ocular route, they are mainly eye drops.

The compounds of the invention are used in these compositions via the topical or ocular route at a concentration generally of between 0.001% and 10% by weight and preferably between 0.01% and 1% by weight relative to the total weight of the composition.

Preferably, the administration of the compound or of the composition according to the invention is carried out topically.

The compounds according to the invention also find an application in cosmetics, in particular in body and hair hygiene and more particularly for cleansing the skin or correcting its odor.

The present invention relates in particular to the use, in an effective amount, of at least one compound chosen from compounds 1 to 45 in a composition as an agent for correcting the odor of the skin, or in or for the preparation of a skin cleansing composition.

The present invention also relates to a cosmetic treatment process for cleansing the skin or correcting its odor, characterized in that a composition comprising at least one compound chosen from compounds 1 to 45 is applied to the skin in an

effective amount.

The composition used in this cosmetic treatment process containing, in a physiologically acceptable support, at least one compound chosen from compounds 1 to 45 may especially be in the form of a cream, a milk, a lotion, a gel, lipid or polymer microspheres or nanospheres or vesicles, a soap or a shampoo.

The concentration of compound chosen from compounds 1 to 45 in the cosmetic compositions is between 0.001% and 3% by weight.

Other characteristics, aspects, objects and advantages of the invention will emerge even more clearly on reading the description which follows, and also the various concrete, but in no way limiting, examples intended to illustrate it.

The compositions according to the invention may, of course, also contain inert or even pharmacodynamically or cosmetically active additives or combinations of these additives and especially: wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizers, for instance glycerol, PEG 400, thiamorpholinone and its derivatives or urea; antiseborrhic or antiacne agents, such as S-carboxymethylcysteine, S-benzylcysteamine, their salts and their derivatives, or benzoyl peroxide;

antibiotics, for instance erythromycin and its esters, neomycin, clindamycin and its esters, and tetracyclines; antifungal agents such as ketoconazole or polymethylene-4,5-isothiazolin-3-ones; agents for promoting the regrowth of hair, for instance Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and its derivatives, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,4-diphenylimidazolidine-2,4-dione); nonsteroidal antiinflammatory agents; carotenoids and especially β-carotene; antipsoriatic agents such as anthralin and its derivatives, and finally eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, their esters and amides or retinoids; D vitamins or derivatives thereof, cortico steroids, free-radical scavengers, α-hydroxy or α-keto acids or their derivatives, or alternatively ion-channel blockers.

These compositions may also contain agents for improving the taste, preserving agents such as para-hydroxybenzoic acid esters, stabilizers, moisture regulators, pH regulators, osmotic pressure modifiers, emulsifiers, UV-A and UV-B screening agents, antioxidants such as α-tocopherol, butylhydroxyanisole or butylhydroxytoluene.

Needless to say, a person skilled in the art will take care to select the optional compound(s) to be added to these compositions such that the advantageous

properties intrinsically associated with the present invention are not, or are not substantially, adversely affected by the envisaged addition.

Several examples of test results of antibacterial activity of the compounds according to the invention and of comparative examples on the bacterium *Staphylococcus aureus*, and also various concrete formulations based on such compounds, will now be given, by way of illustration and with no limiting nature. In the text hereinbelow or hereinabove, the percentages are given by weight unless otherwise mentioned.

EXAMPLE 1

This example illustrates various results of biological tests that show the antibacterial properties of the compounds of the invention on the bacterium *Staphylococcus aureus*.

The method used to determine the minimum inhibitory concentration or MIC is that described in the publication entitled "National committee for clinical laboratory standards" Vol. 13, No. 25, December 1993; Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically-third edition, approved standard". This minimum inhibitory concentration gives an indication as to the bacteriostatic effect of the test compounds,

i.e. the capacity of these compounds to stop the proliferation of the bacterium.

Each compound of the invention was tested at least three times. The average of the test results was calculated, along with the standard deviation. The reference compound used is gentamycin. The results obtained are collated in the following table:

Table II	**MIC results (μM)**	
Compound	**Mean**	**Standard deviation**
Gentamycin	0.11	0.06
1	1.04	0.36
2	1.04	0.36
3	1.04	0.36
4	1.25	0.00
5	1.25	0.00
6	1.25	0.00
7	1.66	0.72
8	1.66	0.72
9	1.66	0.72
10	1.66	0.72
11	2.08	0.72
12	2.08	0.72
13	2.08	0.72
14	2.08	0.72
15	2.50	0.00
16	2.50	0.00

	Table II (continued)	
17	2.50	0.00
18	2.50	0.00
19	2.50	0.00
20	2.50	0.00
21	2.50	0.00
22	2.50	0.00
23	2.50	0.00
24	3.33	1.44
25	3.33	1.44
26	3.33	1.44
27	3.33	1.44
28	3.33	1.44
29	3.33	1.44
30	3.33	1.44
31	3.33	1.44
32	3.33	1.44
33	3.33	1.44
34	3.33	1.44
35	3.33	1.44
36	4.16	1.44
37	4.16	1.44
38	4.16	1.44
39	5.00	0.00
40	5.00	0.00
41	5.00	4.33

	Table II (continued)	
42	5.00	0.00
43	5.00	4.33
44	5.00	0.00
45	5.00	0.00

These results show the antibacterial activity of the compounds according to the invention on the bacterium *Staphylococcus aureus*.

EXAMPLE 2

This example illustrates various results of biological tests that show the superiority of the antibacterial properties of the compounds of the invention on the bacterium *Staphylococcus aureus* compared with retinaldehyde compounds which are described in the French patent application from Pierre Fabre, No. FR 2 736 548.

The method used to determine the MIC values is the same as that described in Example 1 of the present patent application.

The method used to determine the minimum bactericidal concentration, or MBC, corresponds to that described in Bactéricidie, P. Courvalin et al., Editions Maloine, 1990, chapter 7, page 335

This minimum bactericidal concentration gives an indication as to the bactericidal effect of the test compounds, i.e. the capacity of these compounds to kill

the bacterium.

Each compound of the invention and each comparative example derived from the Pierre Fabre patent application No. FR 2 736 548 was tested at least three times. The mean of the test results was calculated, along with the standard deviation. The reference compound used is gentamycin. The results obtained are collated in the following tables:
Comparative example 1 is *all-trans*-retinaldehyde.
Comparative example 2 is 9-*cis*-retinaldehyde.
Comparative example 3 is 13-*cis*-retinaldehyde.

MIC results (μM):

Table III	**MIC results (μM)**	
Compound	**Mean**	**Standard deviation**
Gentamycin	0.14	0.06
Compound 1	1.30	0.45
Compound 5	3.30	2.57
Compound 2	2.45	1.37
Comparative example 1	11.64	5.85
Comparative example 2	11.52	5.95
Comparative example 3	7.64	2.40

These results show that the compounds of the invention show better bacteriostatic activities on the bacterium *Staphylococcus aureus* than the compounds of the prior art.

MBC results (μM):

Table IV	MBC results (μM)	
	Mean	Standard deviation
Gentamycin	0.26	0.05
Compound 1	12.50	0.00
Compound 5	13.18	7.30
Compound 2	16.65	8.33
Comparative example 1	26.33	13.39
Comparative example 2	16.63	4.15
Comparative example 3	15.97	7.89

These results show that the compounds of the invention show bactericidal activities on the bacterium *Staphylococcus aureus* that are equivalent to those of the compounds of the prior art.

Thus, these results show that the compounds of the invention are just as bactericidal on the bacterium *Staphylococcus aureus*, but are much more bacteriostatic than the compounds of the prior art, which means overall that the compounds of the invention have better antibacterial activities on the bacterium *Staphylococcus aureus* than the compounds of the prior art.

EXAMPLE 3

This example illustrates various concrete

formulations based on the compounds according to the invention.

A- ORAL ROUTE

(a) 0.2 g tablet

- Compound 1	0.001 g
- Starch	0.114 g
- Dicalcium phosphate	0.020 g
- Silica	0.020 g
- Lactose	0.030 g
- Talc	0.010 g
- Magnesium stearate	0.005 g

(b) Drinkable suspension in 5 ml ampules

- Compound 5	0.001 g
- Glycerol	0.500 g
- 70% sorbitol	0.500 g
- Sodium saccharinate	0.010 g
- Methyl para-hydroxybenzoate	0.040 g
- Flavoring	qs
- Purified water qs	5 ml

(c) 0.8 g tablet

- Compound 2	0.500 g
- Pregelatinized starch	0.100 g
- Microcrystalline cellulose	0.115 g
- Lactose	0.075 g
- Magnesium stearate	0.010 g

(d) Drinkable suspension in 10 ml ampules

- Compound 4		0.200 g
- Glycerol		1.000 g
- 70% sorbitol		1.000 g
- Sodium saccharinate		0.010 g
- Methyl para-hydroxybenzoate		0.080 g
- Flavoring		qs
- Purified water	qs	10 ml

B- TOPICAL ROUTE

(a) Ointment

- Compound 1	0.020 g
- Isopropyl myristate	81.700 g
- Fluid liquid paraffin	9.100 g
- Silica ("Aerosil 200" sold by Degussa)	9.180 g

(b) Ointment

- Compound 2		0.300 g
- White petroleum jelly codex	qs	100 g

(c) Nonionic water-in-oil cream

- Compound 1	0.100 g
- Mixture of emulsifying lanolin alcohols, waxes and oils ("Anhydrous eucerin" sold by BDF)	39.900 g
- Methyl para-hydroxybenzoate	0.075 g

- Propyl para-hydroxybenzoate	0.075 g
- Sterile demineralized water qs	100 g

(d) Lotion

- Compound 3	0.100 g
- Polyethylene glycol (PEG 400)	69.900 g
- 95% ethanol	30.000 g

(e) Hydrophobic ointment

- Compound 5	0.300 g
- Isopropyl myristate	36.400 g
- Silicone oil ("Rhodorsil 47 V 300" sold by Rhône-Poulenc)	36.400 g
- Beeswax	13.600 g
- Silicone oil ("Abil 300 000 cst" sold by Goldschmidt) qs	100 g

(f) Nonionic oil-in-water cream

- Compound 2	1.000 g
- Cetyl alcohol	4.000 g
- Glyceryl monostearate	2.500 g
- PEG-50 stearate	2.500 g
- Karite butter	9.200 g
- Propylene glycol	2.000 g
- Methyl para-hydroxybenzoate	0.075 g
- Propyl para-hydroxybenzoate	0.075 g
- Sterile demineralized water qs	100 g

CLAIMS

1. The use of an effective amount of at least one compound of retinoid type for the preparation of a composition for preventively or curatively treating bacterial colonizations, said retinoid compound being chosen from:

6-[3-(1-Adamantyl)-4-methoxy-5-hydroxyphenyl]-2-naphthoic acid

4-[4-(6-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(6-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

6-[2-Methyl-4-hydroxy-5-(1-adamantyl)phenyl]-2-naphthoic acid

4-[3-(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dienylidene)prop-1-ynyl]benzoic acid

2-Hydroxy-4-[4-(4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2-[3-(1-Adamantyl)-4-methoxyphenyl)ethynyl]-4-thiophenecarboxylic acid

4-[4-(4,4'-Dimethylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-Hydroxy-2'(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2"-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-

4"-carboxylic acid

6-(3-Adamantan-1-yl-5-bromo-4-hydroxyphenyl)-naphthalene-2-carboxylic acid

4-[4-(6,4'-Dimethylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2'-(4,4-Dimethylthiochroman-6-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2'-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphtho-[2,3-b]thiophen-2-yl)benzoic acid

4-[(6-Hydroxy-7-(1-adamantyl)-2-naphthyl]benzoic acid

4-[2-Nonyloxyimino-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetylamino]benzoic acid

4-[3-Adamantan-1-yl-4-(2-methoxyethoxymethoxy)-phenylethynyl]-2-hydroxybenzoic acid

4-[[3-(1-Adamantyl)-4-[(2-methyl-3-hydroxypropyloxy)phenyl]ethynyl]]benzoic acid

2-Hydroxymethyl-5-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydroanthracen-2-yl)phenol

4-[4-(4'-Propylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2-Hydroxy-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanylethynyl)benzoic acid

2'-(3-Methoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-

carboxylic acid

6-[Butoxy-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)methyl]naphthalene-2-carboxylic acid

4-[3-(1,1-Dimethyldecyl)-4-methoxybenzoylamino]benzoic acid

4-(3-Adamantan-1-yl-4-hexyloxybenzoylamino)benzoic acid

6-[3-(1-Adamantyl)-4-hydroxyphenyl]-2-napthylmethanol

2-Hydroxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydroanthracen-2-yl)benzoic acid

2-(3-Adamantan-1-yl-4-hydroxyphenyl)benzofuran-5-carboxylic acid

4-[6-Methoxyethoxymethoxy-7-(1-adamantyl)-2-naphthyl]salicylic acid

(E)-4-[4-(5-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(3-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanylethynyl)benzoic acid

2-Methoxymethoxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1;4'1"]terphenyl-4"-carboxylic acid

2-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4'1"]terphenyl-4"-carboxylic acid

4-[(Z)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-

naphthyl)-2-undecenamido]benzoic acid

4-[4-(4'-Methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2'-Propoxy-5'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)biphenyl-4-carboxylic acid

4-[2-Heptyloxyimino-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)acetylamino]benzoic acid

6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yloxy)naphthalene-2-carboxylic acid amide

(2-Dimethylaminoethyl)amide of 6-(3-adamantan-1-yl-4-methoxyphenyl)naphthalene-2-carboxylic acid

2-Hydroxy-4-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ylselanylethynyl)benzoic acid

2'-(3-Methoxymethoxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

3-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

3-(5'-Adamantan-1-yl-4'-methoxy-2'-methylbiphenyl-3-yl)acrylic acid.

2. The use of an effective amount of at least one compound of retinoid type chosen from the list of compounds in claim 1, for the preparation of a composition for preventively or curatively treating aggravations of pathologies caused by a bacterial colonization.

3. The use of an effective amount of at least one compound of retinoid type chosen from the list of compounds in claim 1, for the preparation of a composition for preventively or curatively treating cutaneous overinfections induced by bacterial colonization.

4. The use of an effective amount of at least one compound of retinoid type chosen from the list of compounds in claim 1, in or for the preparation of a skin cleansing composition.

5. The use of an effective amount of at least one compound of retinoid type chosen from the list of compounds in claim 1, in a composition as an agent for correcting the odor of the skin.

6. The use as claimed in any one of claims 1 to 4, characterized in that the bacterium responsible for the bacterial colonization is *Staphylococcus aureus*.

7. The use as claimed in any one of claims 1 to 4, characterized in that the bacterium responsible for the bacterial colonization is *Propionibacterium acnes*.

8. The use as claimed in claims 3 and 6, characterized in that the cutaneous overinfection induced by bacterial colonization is "scalded skin syndrome".

9. The use as claimed in claims 2 and 6,

characterized in that the pathology associated with a bacterial colonization is impetigo.

10. The use as claimed in claims 2 and 6, characterized in that the pathology associated with a bacterial colonization is atopic dermatitis.

11. The use as claimed in claim 10, characterized in that the compound is chosen from one of the compounds in the list below:

4-[4-(6-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(6-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[6-Methoxyethoxymethoxy-7-(1-adamantyl)-2-naphthyl]salicylic acid

(E)-4-[4-(5-Methoxymethoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(3-Methoxy-4'-methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

2-Methoxymethoxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4'1"]terphenyl-4"-carboxylic acid

4-[4-(4'-Methylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid

4-[4-(4'-Propylbiphenyl-2-yl)but-3-en-1-ynyl]benzoic acid.

12. The use as claimed in claims 2 and 7, characterized in that the pathology associated with a

bacterial colonization is acne.

13. The use as claimed in claim 12, characterized in that the compound is chosen from one of the compounds in the list below:

6-[3-(1-Adamantyl)-4-methoxy-5-hydroxyphenyl]-2-naphthoic acid

4-[3-(3,5-Di-tert-butyl-4-oxocyclohexa-2,5-dienylidene)prop-1-ynyl]benzoic acid

2-[3-(1-Adamantyl)-4-methoxyphenyl)ethynyl]-4-thiophenecarboxylic acid

4-Hydroxy-2'(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2"-Hydroxy-2'-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

6-(3-Adamantan-1-yl-5-bromo-4-hydroxyphenyl)-naphthalene-2-carboxylic acid

2'-(4,4-Dimethylthiochroman-6-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

2'-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)[1,1';4',1"]terphenyl-4"-carboxylic acid

4-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphtho[2,3-b]thiophen-2-yl)benzoic acid

4-[(6-Hydroxy-7-(1-adamantyl)-2-naphthyl]benzoic acid

14. The use as claimed in any one of the

preceding claims, characterized in that the compound as defined in claim 1 is combined with other compounds with activity of retinoid type, with D vitamins or derivatives thereof, with cortico steroids, with free-radical scavengers, α-hydroxy or α-keto acids or derivatives thereof, or alternatively with ion-channel blockers.

15. The use as claimed in any one of the preceding claims, characterized in that the compound as defined in claim 1 is used in a concentration of between 0.001% and 10% by weight relative to the total weight of the composition.

16. A cosmetic treatment process for cleansing the skin or correcting its odor, characterized in that a composition comprising an effective amount of at least one compound as defined in claim 1, in a physiologically acceptable composition, is applied to the skin.

17. The cosmetic treatment process as claimed in claim 16, characterized in that the concentration of compound as defined in claim 1 is between 0.001% and 3% by weight relative to the total weight of the composition.