US 20200054552A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2020/0054552 A1**

CHANG et al. (43) **Pub. Date: Feb. 20, 2020**

(54) **MEDICAMENT FOR THE TREATMENT OF VIRAL SKIN AND TUMOUR DISEASES**

(71) Applicant: **Medigene AG**, Planegg/Martinsried (DE)

(72) Inventors: **Yunik CHANG**, Sonoma, CA (US); **Robert LATHROP**, Fort Collins, CO (US); **Erwin BOHM**, Ladenburg (DE); **Irene GANDER-MEISTERERNST**, Stockdorf (DE); **Regina GREGER**, Iffeldorf (DE); **Johanna HOLLDACK**, Aarhus C (DK); **Ulrich MOEBIUS**, Gauting-Unterbrunn (DE)

(21) Appl. No.: **16/543,763**

(22) Filed: **Aug. 19, 2019**

Related U.S. Application Data

(63) Continuation of application No. 15/680,819, filed on Aug. 18, 2017, now Pat. No. 10,434,059, which is a continuation of application No. 12/887,250, filed on Sep. 21, 2010, now Pat. No. 9,770,406, which is a continuation of application No. 10/495,889, filed on Sep. 24, 2004, now Pat. No. 7,858,662, filed as application No. PCT/EP02/12919 on Nov. 18, 2002.

(60) Provisional application No. 60/331,705, filed on Nov. 19, 2001.

(30) **Foreign Application Priority Data**

Nov. 19, 2001 (DE) 10156794.4

Publication Classification

(51) **Int. Cl.**

A61K 9/00	(2006.01)
A61K 47/14	(2006.01)
A61K 47/10	(2006.01)
A61K 47/06	(2006.01)
A61K 31/353	(2006.01)
A61K 31/23	(2006.01)

(52) **U.S. Cl.**

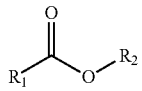
CPC ***A61K 9/0014*** (2013.01); ***A61K 47/14*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/06*** (2013.01); *Y10S 514/934* (2013.01); ***A61K 31/23*** (2013.01); *Y10S 514/947* (2013.01); *Y10S 514/967* (2013.01); *Y10S 514/969* (2013.01); ***A61K 31/353*** (2013.01)

(57) **ABSTRACT**

The invention relates to a medicament containing a compound of general formula (I), where R_1=independently, a straight or branched, saturated, singly- or multiply-unsaturated, optionally substituted C_{11}-C_{21} alkyl, alkylene or alkinyl group, preferably a C_{11}-C_{15} alkyl, alkylene or alkinyl group, particularly a C_{11}-C_{13} alkyl, alkylene or alkinyl group, most preferably a C_{13} alkyl group, R_2=independently, a straight or branched C_1-C_8 alkyl, alkylene or alkinyl group, preferably a C_1-C_6 alkyl, alkylene or alkinyl group, in particular a C_2-C_4 alkyl, alkylene or alkinyl group, most preferably a C_3 alkyl group, a —$[CH_2$—(CH_2)m—$O]_n$H group with n=1 to 10, preferably n=1 to 5, to m=1 to 5, preferably m=1 to 3, a —CH_2—$[CH$—$(OH)]_p$ $[CH_2$—$R_3]$-group, where R_3=independently H or OH, p=1 to 7, preferably p=1 to 4, a pentose group or a hexose group, as therapeutically active agent, alone or in combination with one or several further pharmaceutical agents as a combination preparation for the treatment of viral skin diseases and/or tumor diseases, in particular caused by human papilloma virus (HPV) and/or herpes viruses and a topically acting medicament formulation and the use thereof.

MEDICAMENT FOR THE TREATMENT OF VIRAL SKIN AND TUMOUR DISEASES

[0001] The present invention relates to a pharmaceutical which comprises a compound of the formula



[0002] where R_1, independent of each other, is an unbranched or branched, saturated, singly or multiply unsaturated, optionally substituted C_{11}-C_{21} alkyl, alkylene or alkynyl radical, preferably a C_{11}-C_{15} alkyl, alkylene or alkynyl radical, in particular a C_{11}-C_{13} alkyl, alkylene or alkynyl radical, especially a C_{13}-alkyl radical, and

[0003] R_2 is, independent of each other, an unbranched or branched C_1-C_8 alkyl, alkylene or alkynyl radical, preferably a C_1-C_6 alkyl, alkylene or alkynyl radical, in particular a C_2-C_4 alkyl, alkylene or alkynyl radical, especially a C_3-alkyl radical, a $—[CH_2—(CH_2)_m—O]_n—H$ radical where n=1 to 10, preferably n=1 to 5, m=1 to 5, preferably m=1 to 3,

[0004] a $—CH_2—[CH—(OH)]_p—(CH_2—(R_2)]$ radical, where R_3 is, independent of each other, a hydrogen or a hydroxyl radical, p=1 to 7, preferably p=1 to 4, a pentose radical or a hexose radical,

[0005] as a therapeutically active compound, either alone or together with one or more additional pharmaceutical active compounds as a combination preparation, for treating viral skin diseases and/or tumor diseases which are caused, in particular, by human papilloma viruses (HPV) and/or herpes viruses, and also to a topically acting pharmaceutical formulation and its use.

[0006] Papilloma viruses (HPV) are DNA viruses which infect the epithelial cells of mammals and thereby induce uncontrolled cell growth. There are a very wide variety of papilloma viruses, which infect humans and different animal species. In this connection, all the viral types infect the basal epithelial cells and remain as episomes or integrate their DNA into the host genome.

[0007] It has been known for a long time that papilloma viruses cause genital warts (*Condyloma acuminata*), ordinary and plantar warts, bowenoid papulosis in men and women, and cervical intraepithelial neoplasias in women.

[0008] Depending on the method used, the detection rate for HPV is almost 100%. It is in the main HPV 6 and HPV 11 viruses which are found in warts and genital warts (*Condyloma acuminata*). Since HPV 16 and HPV 18 are principally observed in malignant, desquamative cell carcinomas, as in the case of cancer of the penis and of the uterine cervix, it is generally accepted that HPV 16 and HPV 18 are linked to malignant HPV diseases.

[0009] At present, physical methods are predominantly used for treating genital warts caused by human papilloma viruses. These methods include surgical removal, electrocauterization, cryosurgery and laser therapy to mention but a few. An additional medicinal treatment is the use of Podophyllin, 5-Fluorouracil, Bleomycin, Interferon, Imiquimod, etc.

[0010] Surgical treatment suffers from the disadvantage that it is very unpleasant for the patient and can lead to further infection. Up until now, a topical use has involved the risk of side effects since the active compounds employed possess cytotoxic properties or augment the cellular immune defense and can consequently induce local inflammations. This demonstrates that the therapeutic possibilities which have thus far been available are still not satisfactory.

[0011] In addition to this, there is the fact that the proportion of recurrences is very high in the case of warts and genital warts and complete healing can only be achieved by means of constant and consistent treatment. For this reason, there is a need for a more reliable and comfortable treatment.

[0012] Particularly when treating genital warts, but also in connection with all the other diseases which are caused by the papilloma virus, there is a requirement for a treatment which is easy for the patient to use. For example, a treatment which the patient himself can use at the affected sites and which gives good results in relatively short time, and exhibits only few or no side effects, would be suitable.

[0013] Herpes simplex viruses (HSV) are DNA viruses from the alpha subfamily Herpetoviridae. They are divided into two groups, i.e. HSV 1, termed the oral strain, and HSV 2, termed the genital strain. Herpes simplex viruses penetrate, as a nucleocapsid, into the nerve endings and, using the axonal flow, reach the appurtenant ganglia. They are transmitted by smear and droplet infection from herpes lesions or by healthy chronic carriers. Following a primary infection, the viruses can be reactivated once again, symptomatically or asymptomatically, by irritation, for example due to fever, trauma or radiation, of latently infected neurons. This reactivation depends, in particular, on the defensive condition of the body taken as a whole. Herpes simplex viruses can transform cells neoplastically in animals and in cell cultures. The possibility of an interaction between type 2 herpes simplex viruses and the genesis of cervical carcinomas involving type 16 and type 18 human papilloma viruses is presently being discussed.

[0014] EP 0 087 161 discloses treating herpes infections by treating them with a mixture consisting of isopropyl myristate and small quantities of 4-{lower alkyl}-2,6-(bis-tert-butyl)phenol containing 2,6-(bis-tert-butyl)-4-hydroxytoluene or 4-(lower alkyl)-2,6-(bis-tert-butyl)phenol.

[0015] EP 0 842 660 describes a pharmaceutical composition for treating genital warts which are caused by human papilloma viruses. The composition which is described comprises catechols from tea extracts (*Camellia sinensis*), predominantly (−)-epigallocatechol-gallate in the form of an ointment or a suppository.

[0016] An object of the present invention is therefore to find additional effective antiviral substances and formulations which are suitable for treating viral skin diseases and/or tumor diseases which are caused by papilloma viruses and/or herpes viruses.

[0017] It has now been found, surprisingly, that a pharmaceutical which comprises a compound according to the invention of the formula (I) as the pharmaceutically active compound is suitable for treating viral skin diseases and/or tumor diseases.

[0018] The present invention consequently relates to a pharmaceutical which comprises a compound of the formula (I) as the pharmaceutically active compound,

[0019] where A is a radical of the formula (II)

(II)

[0020] and B is a radical of the formula (III)

(III),

[0021] and

[0022] R_1 is, independent of each other, an unbranched or branched, saturated, singly or multiply unsaturated, optionally substituted C_{11}-C_{21} alkyl, alkylene or alkynyl radical, preferably a C_{11}-C_{15} alkyl, alkylene or alkynyl radical, in particular a C_{11}-C_{13} alkyl, alkylene or alkynyl radical, especially a C_{13}-alkyl radical, and

[0023] R_2 is, independent of each other, an unbranched or branched C_1-C_8 alkyl alkylene or alkynyl radical, preferably a C_1-C_6 alkyl, alkylene or alkynyl radical, in particular a C_2-C_4 alkyl, alkylene or alkynyl radical, especially a C_3 alkyl radical, a —$[CH_2$—$(CH_2)_m$—$O]_n$—H radical where n=1 to 10, preferably n=1 to 5, m=1 to 5, preferably m=1 to 3,

[0024] a —CH_2—$[CH$—$(OH)]_p$—$(CH_2$—$(R_3)]$ radical, where R_3 is, independent of each other, a hydrogen or a hydroxyl radical, p=1 to 7, preferably p=1 to 4, a pentose radical or a hexose radical.

[0025] In this connection, the radical R_1 and/or the radical R_2 can, independent of each other, be substituted by a halogen, preferably fluorine and/or chlorine, or an unbranched or branched C_1-C_6 alkyl, alkylene or alkynyl radical, preferably a C_1-C_3 alkyl, alkylene or alkynyl radical, in particular a methyl radical.

[0026] In this connection, the radical A of the compound (I) can, for example, be derived from hexanoic acid (caproic acid), heptanoic acid, octanoic acid (caprylic acid), nonanoic acid, decanoic acid (capric acid), undecanoic acid, dodecanoic acid (lauric acid), tridecanoic acid, tetradecanoic acid (myristic acid), pentadecanoic acid, hexadecanoic acid (palmitic acid), heptadecanoic acid, octadecanoic acid (stearic acid), nonadecanoic acid, eicosanoic acid, heneicosanoic acid, oleic acid, linoleic acid, linolenic acid and/or arachidonic acid, preferably from caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid and/or arachidonic acid, particularly preferably from myristic acid.

[0027] The radical B of the compound (I) can, for example, be derived from an unbranched or branched C_1-C_8 alkyl alcohol, in particular ethanol, propanol, isopropanol, n-butanol, tert-butanol, particularly preferably isopropanol, ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, glycerol, polyglycerol, a pentose sugar, such as arabitol, adonitol and xylitol, or a hexose sugar, such as sorbitol, mannitol or dulcitol, preferably from ethanol, propanol, isopropanol, butanol, ethylene glycol, polyethylene glycol, propylene glycol, polypropylene glycol, glycerol, polyglycerol, arabitol, adonitol, xylitol, sorbitol, mannitol and/or dulcitol.

[0028] The compound (I) is preferably isopropyl laureate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, ethyl myristate, propyl myristate, butyl myristate and/or ethyl oleate, in particular isopropyl myristate.

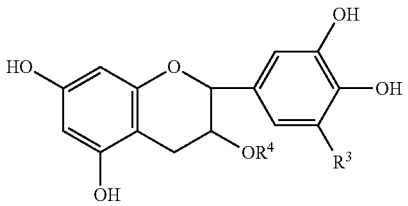
[0029] In another preferred embodiment, the compound (I) is a hydrophobic compound. According to the present invention, a hydrophobic compound is understood as being a compound whose solubility in water is at most approx. 0.2 mg/ml, in particular at most approx. 0.1 mg/ml.

[0030] The pharmaceutical comprises, for example, at least approx. 5%-75% (w/w), preferably at least approx. 10%-60% (w/w), in particular at least approx. 25%-55% (w/w), and especially at least approx. 35%-50% (w/w) of the compound of the formula (I).

[0031] In this connection, the pharmaceutical according to the invention can also contain one or more additional pharmaceutical active compounds as a combination preparation for use which is simultaneous, separate or staggered in time. In this context, preference is given to employing, as additional pharmaceutical active compounds, those compounds which can be used for treating viral skin diseases and/or tumor diseases, such as podophyllin, 5-fluorouracil, bleomycin, interferon or imiquimod, and/or mixtures which comprise at least one catechol.

[0032] In a preferred embodiment, the additional pharmaceutical active compound is an amphiphilic or amphipathic active compound. An amphiphilic or amphipathic active compound is understood as being an active compound which is composed of two functional moieties, in particular one hydrophilic moiety and one lipophilic moiety. This property might, in particular, be able to facilitate the passage of the substance through the skin and achieve an improved effect. In this connection, the improved effect may be attributable, for example, to a longer dwell time at the desired site or to a reduction in the dose of the active compound.

[0033] In a further preferred embodiment, the additional pharmaceutical active compound comprises at least one catechol of the formula (IV)

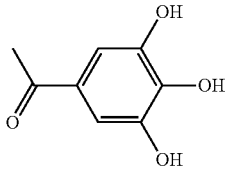


(IV)

[0034] in which

[0035] R_3 is —H or —OH, and

[0036] R_4 is —H or a group of the formula (V)



(V)

[0037] The catechols which are added in this connection may be obtained either synthetically or from natural sources. The natural sources which may especially be mentioned are tea plants. In this context, the natural constituents may be present in differing concentrations depending on the species

and variety. In this connection, the catechols which are employed are preferably isolated from *Camellia sinensis, Camellia asamica, Camellia bohea, Camellia chinensis* or *Camellia oleosa*. All the components of tea plants, in particular the leaves, can be used for isolating the catechols. The catechols which are employed are preferably isolated from a tea extract.

[0038] The catechols which are employed in the present invention are preferably epicatechol, epicatechol gallate, epigallocatechol, epigallocatechol gallate, gallocatechol and gallocatechol gallate, in particular (−)-epicatechol, (−)-epicatechol gallate, (−)-epigallocatechol, (−)-epigallocatechol gallate, (+)-gallocatechol and (−)-gallocatechol gallate.

[0039] The catechols can be used both individually and in the form of mixtures having different compositions. A catechol mixture contains approx. 2-20% (w/w), preferably approx. 4-15% (w/w), in particular approx. 10-11% (w/w) of (−)-epicatechol, approx. 2-20% (w/w), preferably approx. 5-15% (w/w), in particular approx. 5-7% (w/w) of (−)-epicatechol gallate, approx. 1-25% (w/w), preferably approx. 3-15% (w/w), in particular approx. 5-7% (w/w) of (−)-epigallocatechol, approx. 40-75% (w/w), preferably approx. 57-67% (w/w), in particular approx. 61-66% (w/w) of (−)-epigallocatechol gallate, approx. 0.05-5% (w/w), preferably approx. 0.1-1% (w/w), in particular approx. 0.1-0.6% (w/w) of (+)-gallocatechol and/or approx. 0.5-20% (w/w), preferably approx. 1-10% (w/w), in particular approx. 1-5% (w/w) of (−)-gallocatechol gallate.

[0040] In a preferred embodiment, the catechol mixture is composed of approx. 5.9% (w/w) of (−)-epicatechol, approx. 12.6% (w/w) of (−)-epicatechol gallate, approx. 17.6% (w/w) of (−)-epigallocatechol, approx. 53.9% (w/w) of (−)-epigallocatechol gallate and/or approx. 1.4% (w/w) of (−)-gallocatechol. A composition of this nature is known under the name Polyphenon® 100.

[0041] In a particularly preferred embodiment, the catechol mixture is composed of approx. 10.8% (w/w) of (−)-epicatechol, approx. 6.5% (w/w) of (−)-epicatechol gallate, approx. 9.2% (w/w) of (−)-epigallocatechol, approx. 54.8% (w/w) of (−)-epigallocatechol gallate and/or approx. 4.0% (w/w) of (−)-gallocatechol gallate. A composition of this nature is known under the name Polyphenon® E.

[0042] The pharmaceutical according to the invention comprises, for example, approx. 1-30% (w/w), preferably approx. 2-20% (w/w) and, in particular, approx. 15-18% (w/w) of a catechol and at least approx. 5-90% (w/w), preferably at least approx. 10-70% (w/w), in particular at least approx. 25-60% (w/w) and, especially, at least approx. 35-50% (w/w) of the compound (I).

[0043] The familiar methods of pharmaceutical technology are used, in a customary manner, for preparing pharmaceuticals which comprise one or more compounds according to the invention and/or for using these pharmaceuticals in the application according to the invention. For this, the active compounds are worked up, together with suitable, pharmaceutically acceptable auxiliary substances and carrier substances, into the medicinal forms which are suitable for the different indications and sites of administration. In this context, the pharmaceuticals can be prepared such that the rate of release in each case desired, for example a rapid accumulation and/or a delayed-release or depot effect, is achieved.

[0044] Customary emulsions, gels, ointments, creams of the mixed-phase or amphiphilic emulsion systems (oil/water-water/oil mixed phase), and also liposomes and transfersomes or plasters, preferably ointments and creams, particularly preferably an ointment, may be mentioned for conventional application to the skin or mucosa. The active compound is preferably applied locally in the region in which there is a skin or mucosal change and/or disease.

[0045] In addition to the known uses on the skin and/or mucosa, the following are suitable for use as special pharmaceutical preparations which can be administered topically, locally or regionally: emulsions, creams, ointments, effervescent tablets or suppositories which can be administered genitally, vaginally or rectally, in particular genitally and vaginally. Rectal capsules can also be prepared on the basis of gelatin or other carrier substances. Suitable suppository bases are hardened fats, such as Witepsol®, Massa Estarium®, Novata®, coconut butter, glycerol/gelatin pastes, glycerol/soap gels and polyethylene glycols.

[0046] Examples of suitable auxiliary and/or carrier substances are sodium alginate, as a gelatinizing agent for preparing a suitable base, or cellulose derivatives, such as guar or xanthan gum, inorganic gelatinizing agents, such as aluminum hydroxide or bentonites (what are termed thixotropic gel-formers), polyacrylic acid derivatives, such as Carbopol®, polyvinylpyrrolidone, microcrystalline cellulose and carboxymethylcellulose. Amphiphilic low molecular weight and higher molecular weight compounds, and also phospholipids, are also suitable. The gels can be present either as water-based hydrogels or as hydrophobic organogels, for example based on mixtures of low and high molecular weight paraffin hydrocarbons and vaseline. The hydrophilic organogels can be prepared, for example, on the basis of high molecular weight polyethylene glycols. These gelatinous forms are washable. However, the organogels which are preferred are the hydrophobic organogels. Particular preference is given to hydrophobic auxiliary substances and additives, such as petroleum jelly, wax, oleyl alcohol, propylene glycol monostearate and propylene glycol monopalmitostearate. It is, of course, likewise possible to add skin-sedating and/or inflammation-inhibiting additives which are known to the skilled person, such as synthetically prepared active compounds and/or extracts and/or active compounds from medicinal plants, in particular bisobolol and panthenol. It is furthermore also possible to add dyes, for example yellow and/or red iron oxide and/or titanium dioxide for the purpose of matching as regards color.

[0047] Emulsifiers which can be employed are anionic, cationic or neutral surfactants, for example alkali metal soaps, metal soaps, amine soaps, sulfonated compounds, invert soaps, higher fatty alcohols, partial fatty acid esters of sorbitan and polyoxyethylene sorbitan, e.g. lanette types, wool wax, lanolin or other synthetic products for preparing the oil/water and/or water/oil emulsions.

[0048] It is possible to use vaseline, natural or synthetic waxes, fatty acids, fatty alcohols, fatty acid esters, for example as monoglycerides, diglycerides or triglycerides, paraffin oil or vegetable oils, hydrogenated castor oil or coconut oil, hog fat, synthetic fats, for example based on, caprylic acid, capric acid, lauric acid or stearic acid, such as Softisan®, or triglyceride mixtures, such as Miglyol®, can be used as lipids, in the form of fatty and/or oleaginous and/or waxy components for preparing the ointments, creams or emulsions.

[0049] It is possible to use, for example, osmotically active acids and alkaline solutions, for example hydrochloric acid, citric acid, sodium hydroxide solution, potassium hydroxide solution, sodium hydrogen carbonate, and, in addition, buffer systems, such as citrate, phosphate, tris buffer or triethanolamine, for adjusting the pH. It is possible to add preservatives as well, such as methyl benzoate or propyl benzoate (parabens) or sorbic acid, for increasing the stability.

[0050] Pastes, powders and solutions may be mentioned as additional forms which can be applied topically. As consistency-imparting bases, the pastes frequently contain hydrophobic and hydrophilic auxiliary substances, preferably, however, hydrophobic auxiliary substances containing a very high proportion of solids. In order to increase dispersity, and also flowability and slipperiness, and also to prevent agglomerates, the powders or topically applicable powders can, for example, contain starch species, such as wheat or rice starch, flame-dispersed silicon dioxide or siliceous earth, which also serve as diluent.

[0051] The medicinal forms which are in each case suitable can be produced on the basis of pharmaceutico-physical principles in conformity with formulation guidelines and methods known to a skilled person.

[0052] The pharmaceutical according, to the invention preferably comprises approx. 35% (w/w) of isopropyl myristate, approx. 15% (w/w) of at least one catechol, approx. 24.5% (w/w) of petroleum jelly, approx. 20% (w/w) of wax, approx. 5% (w/w) of propylene glycol monostearate or propylene glycol monopalmitostearate and approx. 0.5% (w/w) of oleyl alcohol.

[0053] The pharmaceutical of the present invention and/or of a pharmaceutical metabolites is used in the treatment of viral skin diseases and/or tumour diseases.

[0054] The term pharmaceutical metabolite is to be understood as meaning one or more compounds which arise during use as a result of biological metabolism. These metabolites can be intermediates arising during intermediary metabolism or the end products of metabolism. The metabolites are preferably metabolic products which arise as a result of application to the skin and/or mucosa, in particular hydrolysis products of the compound having the formula (I). Conceivable hydrolysis products can be derived, for example, from radical A and/or radical B.

[0055] Viral skin diseases are understood as being skin diseases which are induced or caused by viruses and/or associated with viral infections. They include, for example, skin diseases such as warts, genital warts, benign tumors of the skin and/or mucosa which are caused by papilloma viruses, for example verrucae plantares, verrucae vulgares, verrucae planae juveniles, epidermodysplasia verruciformis, *Condylomata acuminata, Condylomata plana*, bowenoid papulosis, papillomas on the larynx and oral mucosa, focal epithelial hyperplasia, herpes labialis, Kaposi's sarcoma, varicella and shingles.

[0056] These viral skin diseases and/or tumor diseases are caused by at least one papilloma virus or viruses, in particular human papilloma viruses, such as HPV 1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19-29, 31, 32, 34, 36-38, 46-50, 56, 58, by at least one herpes virus or herpes viruses, such as herpes simplex virus 1, herpes simplex virus 2, varicella zoster virus or human herpes virus, such as 1, 2, 3, 4, 7 or 8.

[0057] The figures and the following examples are intended to clarify the invention without restricting it. Skilled persons can modify the invention appropriately, within the bounds of customary ability, without departing from the protective scope.

EXAMPLES

[0058] Clinical Study for Comparing an Ointment and a Cream Containing Isopropyl Myristate

[0059] 93 patients (in each case divided equally into men and women) took part in a multicenter clinical study which was carried out at a total of 30 different centers in Germany and Russia. The study was randomized and performed double-blind. The study examined the clinical efficacy of two different formulations of isopropyl myristate (an ointment and a cream) in the treatment of external genital warts.

[0060] The formulations which were tested had the following compositions:

Cream 1

Substance	Quantity (in % w/w)
Cera alba	6.996
Monomuls	2.798
Lameform TGI	5.598
Cetiol V	6.996
Isopropyl myristate	13.992
Tocopherol	0.699
Controx KS	0.066
Glycerol	6.996
Disodium EDTA	0.001
Magnesium sulfate	1.399
D-Panthenol	0.699
Purified water	53.678
Red Iron Oxide*	0.025
Yellow Iron Oxide*	0.054

*The dyes were added for matching as regards color.

Ointment 1

Substance	Quantity (in % w/w)
White Petrolatum, USP	34.023
White Wax, NF	25.000
Isopropyl Myristate, NF	35.000
Oleyl Alcohol, NF	0.500
Propylene Glycol Monostearate, NF	5.000
Red Iron Oxide*	0.022
Yellow Iron Oxide*	0.055
Titanium Dioxide, USP*	0.400

*The dyes were added for matching as regards color.

[0061] The patients applied the topical study medication three times daily or until the genital warts had completely healed or for a maximum of twelve weeks.

[0062] The following data were collected during the study:

[0063] Complete healing (in %)

	Cream 1	Ointment 1
Male	39.1	42.1
Female	35.0	33.3

[0064] Partial healing (in %); this corresponds to at least 75% healing based on the total area of the genital warts.

	Cream 1	Ointment 1
Male	43.5	63.2
Female	50.0	52.4

[0065] The results of the study show that a surprisingly high degree of complete healing, or partial healing, takes place as compared with the placebo values from similar studies using different formulations, in association with which the spontaneous regression of genital warts is approx. 20% in the case of women and approx. 5% in the case of men (Aldara™ (Imiquimod) Cream, 5% Product Monograph, marketed by 3M Pharmaceuticals, Northridge, Calif., Beutner K R et al. (1998) J Am Acad Dermatol 38, 230-9, Edwards L et al. (1998) Arch Dermatol 134 (1); 25-30).

[0066] This therapeutic effect is attributed to the isopropyl myristate, an antiviral effect of which has consequently been demonstrated for the first time.

[0067] Clinical Study for Comparing an Ointment and a Cream Containing Isopropyl Myristate and Polyphenon® E

[0068] 272 patients (equally divided between men and women in each case) took part in a multicenter clinical study which was carried out at a total of 30 different centers in Germany and Russia. The study was randomized and performed double-blind. The study examined the clinical efficacy of two different formulations of isopropyl myristate and Polyphenon® E (an ointment and a cream), as against the formulations from Example 1 containing isopropyl myristate, in the treatment of external genital warts.

[0069] The Polyphenon® E-containing formulations which were tested had the following compositions:

Cream 2	
Substance	Quantity (in % w/w)
Polyphenon ® E	10.000
Cera alba	5.263
Monomuls	2.105
Lameform TGI	4.211
Cetiol V	5.263
Isopropyl myristate	10.526
Tocopherol	0.526
Controx KS	0.050
Glycerol	5.263
Disodium EDTA	0.001
Magnesium sulfate	1.053
D-Panthenol	0.526
Purified water	55.213

Ointment 2	
Substance	Quantity (in % w/w)
Polyphenon ® E	15.000
White Petrolatum, USP	24.500
White Wax, NF	20.000
Isopropyl Myristate, NF	35.000
Oleyl Alcohol, NF	0.500
Propylene Glycol Monostearate, NF	5.000

[0070] The patients applied the topical study medication three times daily or until the genital warts had completely healed or for a maximum of twelve weeks.

[0071] During the study, the following data were collected:

[0072] Complete healing (in %)

	Cream 1	Cream 2	Ointment 1	Ointment 2
Male	39.1	53.9	42.1	61.0
Female	35.0	39.5	33.3	56.8

[0073] Partial healing (≥75% in %)

	Cream 1	Cream 2	Ointment 1	Ointment 2
Male	43.5	64.2	63.2	80.5
Female	50.0	47.4	52.4	81.1

[0074] Analysis of the study shows that, when comparing ointment 1 and cream 1, on the one hand, and ointment 2 and cream 2, on the other hand, the combination of isopropyl myristate and Polyphenon® E leads to a surprising increase in the efficacy of the pharmaceutical.

[0075] If the efficacy of ointment 2 is now compared with that of cream 2, it then becomes evident that ointment 2 is markedly more effective than cream 2. This suggests a synergistic effect between the Polyphenon® E and the isopropyl myristate in the hydrophobic ointment.

[0076] As a result of this synergistic effect, the individual active compounds in the formulation can, in order to achieve the same effect, be employed in substantially smaller quantities than the corresponding individual components. Consequently, the use of this synergistic formulation has advantages not only with regard to the effect but also with regard to the cost of preparing this formulation, something which in turn can have a positive effect on the cost of treating the patient.

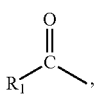
1. A pharmaceutical composition comprising:

(i) a compound having the formula

A-B (I),

wherein A is a radical having the formula

(II)



and wherein B is a radical having the formula

—O—R_2 (III),

and wherein R_1 is, independent of each other, an unbranched or branched, saturated, singly or multiply unsaturated, optionally substituted C_{13}-C_{21} alkyl, alkylene, or alkynyl radical, and R_2 is, independent of each other, an unbranched or branched C_1-C_8 alkyl, alkylene, or alkynyl radical; and

(ii) a mixture of catechols comprising 4-15% (w/w) of (−)-epicatechol, 2-20% (w/w) of (−)-epicatechol gallate, 3-15% (w/w) of (−)-epigallocatechol, 40-75%

(w/w) of (−)-epigallocatechol gallate, 0.1-1% (w/w) of (+)-gallocatechol, and 1-10% (w/w) of (−)-gallocatechol gallate; and

wherein the pharmaceutical comprises at least 5-50% (w/w) of the compound of formula (I).

2. The pharmaceutical composition of claim **1**, wherein said pharmaceutical composition comprises 1-30% (w/w) of said mixture of catechols and at least 10-50% (w/w) of said compound of formula (I).

3. The pharmaceutical composition of claim **2**, wherein said pharmaceutical composition comprises 2-20% (w/w) of said mixture of catechols.

4. The pharmaceutical composition of claim **3**, wherein said pharmaceutical composition comprises 15-18% (w/w) of said mixture of catechols.

5. The pharmaceutical composition of claim **2**, wherein said pharmaceutical composition comprises at least 25-50% (w/w) of said compound of formula (I).

6. The pharmaceutical composition of claim **5**, wherein said pharmaceutical composition comprises at least 35-50% (w/w) of said compound of formula (I).

7. The pharmaceutical composition of claim **1**, wherein said mixture of catechols comprises 5-7% (w/w) of said (−)-epicatechol gallate.

8. The pharmaceutical composition of claim **1**, wherein said mixture of catechols comprises 0.1-0.6% (w/w) of said (+)-gallocatechol.

9. The pharmaceutical composition of claim **1**, wherein said mixture of catechols comprises 1-5% (w/w) of said (−)-gallocatechol gallate.

10. The pharmaceutical composition of claim **1**, wherein said mixture of catechols comprises 10.8% (w/w) of (−)-epicatechol, 6.5% (w/w) of (−)-epicatechol gallate, 9.2% (w/w) of (−)-epigallocatechol, 54.8% (w/w) of (−)-epigallocatechol gallate, and/or 4.0% (w/w) of (−)-gallocatechol gallate.

11. The pharmaceutical composition of claim **1**, wherein said pharmaceutical composition comprises at least 10-50% (w/w) of said compound of formula (I).

12. The pharmaceutical composition of claim **11**, wherein said pharmaceutical composition comprises at least 25-50% (w/w) of said compound of formula (I).

13. The pharmaceutical composition of claim **12**, wherein said pharmaceutical composition comprises at least 35-50% (w/w) of said compound of formula (I).

14. The pharmaceutical composition of claim **1**, wherein said catechols are isolated from a tea extract.

15. The pharmaceutical composition of claim **1**, wherein one or more additional pharmaceutical compound(s) is/are administered simultaneously or separately.

16. The pharmaceutical composition of claim **15**, wherein said one or more additional pharmaceutical compound(s) is/are amphiphilic.

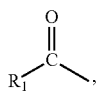
17. The pharmaceutical composition of claim **1**, further comprising additives and/or auxiliary substances.

18. The pharmaceutical composition of claim **17**, wherein said additives and/or auxiliary substances are hydrophobic and are selected from the group consisting of petroleum jelly, wax, oleyl alcohol, propylene glycol monostearate, and propylene glycol monopalmitostearate.

19. A pharmaceutical composition comprising 35% (w/w) of a compound having the formula

$$A\text{-}B \qquad (I),$$

wherein A is a radical having the formula



(II)

and wherein B is a radical having the formula

$$—O—R_2 \qquad (III),$$

and wherein R_1 is, independent of each other, an unbranched or branched, saturated, singly or multiply unsaturated, optionally substituted C_{13}-C_{21} alkyl, alkylene, or alkynyl radical, and R_2 is, independent of each other, an unbranched or branched C_1-C_8 alkyl, alkylene, or alkynyl radical;

and wherein said pharmaceutical composition further comprises 15% (w/w) of a mixture of catechols comprising 4-15% (w/w) of (−)-epicatechol, 2-20% (w/w) of (−)-epicatechol gallate, 3-15% (w/w) of (−)-epigallocatechol, 40-75% (w/w) of (−)-epigallocatechol gallate, 0.1-1% (w/w) of (+)-gallocatechol, 1-10% (w/w) of (−)-gallocatechol gallate, 24.5% (w/w) of petroleum jelly, 20% (w/w) of wax, 5% (w/w) of propylene glycol monostearate or propylene glycol monopalmitostearate, and 0.5% (w/w) of oleyl alcohol.

20. A method of treating a papilloma virus-induced skin disease or benign tumor disease in a patient, said method comprising administering to a patient a pharmaceutical composition of claim **1**.

21. The method of claim **20**, wherein said papilloma virus-induced skin disease or benign tumor disease is caused by HPV 1, 2, 3, 4, 5, 6, 8, 9, 11, 12, 13, 14, 15, 16, 17, 18, 19-29, 31, 32, 34, 36-38, 46-50, 56, or 58.

22. The method of claim **20**, wherein said papilloma virus-induced skin diseases are warts or genital warts and the papilloma virus-induced benign tumors are of the skin and/or mucosa.

23. The method of claim **22**, wherein said papilloma virus-induced benign tumors of the skin and/or mucosa are verrucae plantares, verrucae vulgares, verrucae planae juveniles, epidermodysplasia verruciformis, *Condylomata acuminata, Condylomata plana*, bowenoid papulosis, papillomas on the larynx and oral mucosa, or focal epithelial hyperplasia.

24. The method of claim **20**, wherein said pharmaceutical composition is applied topically.

25. The method of claim **24**, wherein said pharmaceutical composition is applied genitally or vaginally.

* * * * *