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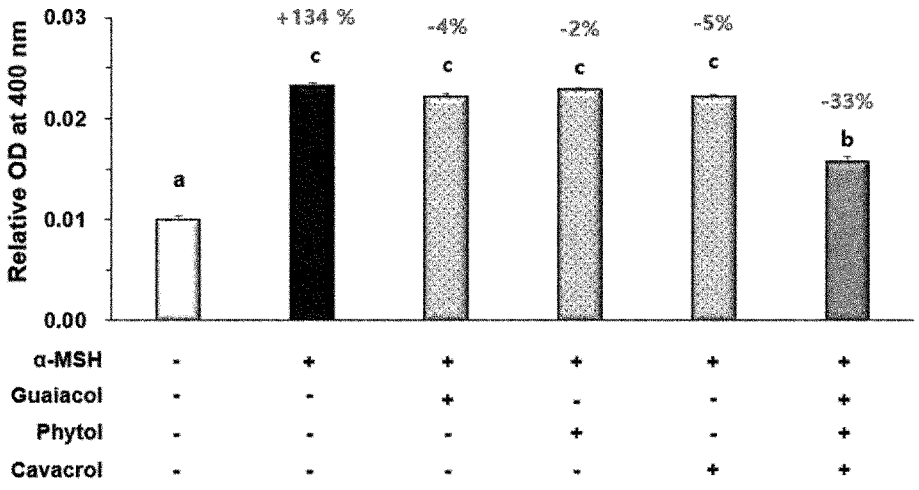
(54) Title: COMPOSITION FOR SKIN WHITENING COMPRISING GUAIACOL, PHYTOL AND CARVACROL AS ACTIVE INGREDIENTS



(57) Abstract: The present invention relates to a composition for skin whitening, including guaiacol, phytol and carvacrol as active ingredients, and more particularly, to a composition for skin whitening that contains guaiacol, phytol and carvacrol as active ingredients and may exhibit an excellent melanogenesis inhibitory effect. The composition according to the present invention may have an excellent inhibitory effect on melanogenesis induced by melanocyte-stimulating hormone (αMSH), and may be used in various applications for cosmetics, health functional food, medicines or quasi-drugs due to being safe for the human body and few side effects.

WO 2020/197255 A1

Description

Title of Invention: COMPOSITION FOR SKIN WHITENING COMPRISING GUAIACOL, PHYTOL AND CARVACROL AS ACTIVE INGREDIENTS

Technical Field

[1] This application claims priority to and the benefit of Korean Patent Application No. 10-2019-0033720, filed on March 25, 2019, the disclosure of which is incorporated herein by reference in its entirety.

[2] The present invention relates to a composition for skin whitening, which includes guaiacol, phytol and carvacrol as active ingredients, and more particularly, to a composition for skin whitening which contains guaiacol, phytol and carvacrol as active ingredients and thus may exhibit an excellent melanogenesis inhibitory effect.

Background Art

[3] Human skin color is determined according to amounts of melanin, carotenes and hemoglobin, and among these, melanin acts as a major factor determining skin color. Melanin is known to be produced in melanocytes present in the epidermis of the skin, and then migrate into surrounding keratinocytes, exhibiting skin color. In addition, melanin serves to protect the skin by preventing skin damage caused by UV rays and removing reactive oxygen species (ROS). However, chronic UV exposure is known to cause pigmentation by promoting melanogenesis in melanocytes.

[4] Melanogenesis is initiated in melanosomes in melanocytes. When the skin is exposed to external stress such as UV rays, a production amount of α-melanocyte stimulating hormone (α-MSH) in the melanocytes increases, and α-MSH is known to be bonded with the melanocortin 1 receptor (MC1R), which is a membrane receptor expressed only in melanocytes to activate adenylyl cyclase, thereby amplifying cyclic adenosine monophosphate (cAMP) in cells. When an intracellular cAMP level increases, the cAMP response element binding protein (CREB) is phosphorylated by activation of protein kinase A (PKA), and thus the expression of the microphthalmia transcription factor (MITF) increases. MITF is a major transcription factor in melanogenesis and increases the level of tyrosinase, which is a main enzyme of melanogenesis, and the tyrosinase is well known for acting in the early stage of melanogenesis to regulate a rate of the melanogenesis. According to the above-described pathway, the melanogenesis in melanocytes is performed by complicated steps mediated by enzymes such as MITF, tyrosinase, etc.

[5] The inventors had conducted research on materials having an excellent skin whitening effect, confirming that an excellent melanogenesis inhibitory effect can be

obtained by the use of guaiacol, phytol and carvacrol in combination, and thus the present invention was completed.

[6] [Prior art document]

[7] (Patent Document 0001) Korean Unexamined Patent Application No. 10-2018-0117252

Disclosure of Invention

Technical Problem

[8] The present invention is directed to providing a cosmetic composition for skin whitening, which includes guaiacol, phytol and carvacrol, or cosmetologically acceptable salts thereof as active ingredients.

[9] The present invention is also directed to providing a skin whitening composition for external use, which includes guaiacol, phytol and carvacrol, or salts thereof as active ingredients.

[10] The present invention is also directed to providing a health functional food composition for skin whitening, which includes guaiacol, phytol and carvacrol, or sitologically acceptable salts thereof as active ingredients.

[11] The present invention is also directed to providing a pharmaceutical composition for preventing or treating skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[12] The present invention is also directed to providing a quasi-drug composition for preventing or improving skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[13] However, technical problems to be solved in the present invention are not limited to the above-described problems, and other problems which are not described herein will be fully understood by those of ordinary skill in the art from the following descriptions.

Solution to Problem

[14] The present invention provides a cosmetic composition for skin whitening, which includes guaiacol, phytol and carvacrol, or cosmetologically acceptable salts thereof as active ingredients.

[15] The active ingredients may inhibit the expression of MITF or tyrosinase.

[16] The active ingredients may inhibit melanogenesis induced by α-MSH.

[17] The composition may be prepared in any one form selected from the group consisting of a skin lotion, a skin softener, a skin toner, an astringent, a lotion, a milk lotion, a moisturizing lotion, a nourishing lotion, a massage cream, a nourishing cream, a moisturizing cream, a hand cream, an essence, a pack, a mask pack, a mask sheet, an exfoliate, a soap, a shampoo, a cleansing foam, a cleansing lotion, a cleansing cream, a

body lotion, a body cleanser, an emulsion, a pressed powder, a loose powder and an eye shadow.

[18] The active ingredients may be included at 0.0001 to 20 wt% with respect to the total weight of the cosmetic composition.

[19] The composition may include 20 to 200 parts by weight of phytol and 20 to 200 parts by weight of carvacrol with respect to 100 parts by weight of guaiacol.

[20] In addition, the present invention provides a skin whitening formulation for external use, which includes guaiacol, phytol and carvacrol, or salts thereof as active ingredients.

[21] In addition, the present invention provides a health functional food composition for skin whitening, which includes guaiacol, phytol and carvacrol, or sitologically acceptable salts thereof as active ingredients. The composition may be prepared in any one dosage form selected from the group consisting of a tablet, a granule, a powder, a capsule, a liquid solution and a pill.

[22] In addition, the present invention provides a pharmaceutical composition for preventing or treating skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[23] In addition, the present invention provides a quasi-drug composition for preventing or improving skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[24] The present invention also provides a method for preventing or treating skin pigmentation, the method comprising administering a composition comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients, or allowing it to be taken, to a subject.

[25] The present invention also provides a use of a composition for preventing or treating skin pigmentation, the composition comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

Advantageous Effects of Invention

[26] A composition according to the present invention, which includes guaiacol, phytol and carvacrol as active ingredients, has an excellent effect of inhibiting melanogenesis induced by αMSH, is safe for the human body and has few side effects, and thus can be widely used as materials for cosmetics, health functional food, medicines or quasi-drugs.

Brief Description of Drawings

[27] The above and other objects, features and advantages of the present invention will become more apparent to those of ordinary skill in the art by describing in detail exemplary embodiments thereof with reference to the accompanying drawings, in

which:

[28] FIG. 1 is a graph showing the change in production amounts of melanin in B6F10 melanocytes treated with guaiacol, phytol and carvacrol (each value is the average of 3 test scores ±SEM; the letter on a bar indicates a statistically significant difference at $P<0.05$; one-way ANOVA);

[29] FIG. 2 shows the result of analyzing the change in colors of pellets of B6F10 melanocytes treated with guaiacol, phytol and carvacrol; and

[30] FIG. 3 is a graph showing the change in gene expression of B6F10 melanocytes treated with guaiacol, phytol and carvacrol (each value is the average of 3 test scores ±SEM; the letter on a bar indicates a statistically significant difference at $P<0.05$; one-way ANOVA).

Best Mode for Carrying out the Invention

[31] The inventors confirmed a significantly excellent whitening effect when a combination of guaiacol, phytol and carvacrol was used, and thus the present invention was completed.

[32] Hereinafter, the present invention will be described in detail.

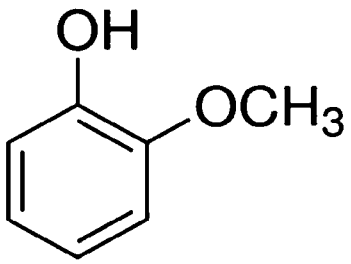
[33] The present invention provides a composition for skin whitening, which includes guaiacol, phytol and carvacrol, or salts thereof as active ingredients.

[34] The active ingredient may include the expression of MITF or tyrosinase. In addition, the active ingredients may inhibit melanogenesis induced by αMSH.

[35] The composition may include 20 to 200 parts by weight of phytol and 20 to 200 parts by weight of carvacrol with respect to 100 parts by weight of guaiacol.

[36] Guaiacol is a phenol-based compound, and is also called 2-methoxyphenol. The chemical formula of guaiacol is $C_7H_8O_2$, the molecular weight thereof is 124.1 g/mol, and the structure thereof is shown in Formula 1 below. Guaiacol is a white-pale yellow crystal or colorless-pale yellow liquid with a unique fragrance and sweetness, and well dissolved in ethanol. Guaiacol becomes black upon exposure to air or light, and its biologically active effects are not known yet. Guaiacol is registered as a flavoring agent in the Food and Drug Administration (FDA) and commercially used to produce the flavor of vanillin. In an oral toxicity test for rats, an LD50 value was reported to be 621 mg/kg, and in a transdermal toxicity test for rabbits, an LD50 value is known to be 4,600 mg/kg.

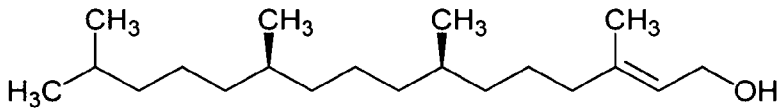
[37] [Formula 1] Molecular structure of guaiacol

[38] 

[39]

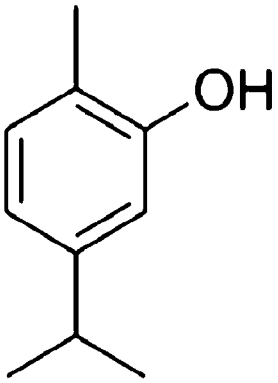
[40] Phytol is a terpene-based compound, and is known to be used as a synthetic raw material of vitamin E. The chemical formula of phytol is $C_{20}H_{40}O$, the molecular weight thereof is 128.2 g/mol, and the structure thereof is shown in Formula 2 below. Phytol is a colorless liquid with a unique fragrance, and is well dissolved in ethanol. In terms of a biologically active function of phytol, which has been reported to date, phytol acts as a ligand of peroxisome proliferator-activated receptor alpha (PPAR-α), which is a transcription factor, to change fatty acid metabolism, and no skin whitening function has been reported yet. Phytol is registered as a flavoring agent in the Korea Food and Drug Administration (KFDA), and mainly used commercially in cosmetics, shampoos, soaps and detergents. In an oral toxicity test for rats, an LD50 value was reported to be 5,000 mg/kg or more, and in a transdermal toxicity test for rabbits, an LD50 value is known to be 5,000 mg/kg or more.

[41] [Formula 2] Structure of phytol

[42] 

[43] Carvacrol is a terpene-based compound, and also called isopropyl-2-methylphenol, and is known to be commonly present in, mainly, peppermint, oregano, bergamot, etc. The chemical formula of carvacrol is $C_{10}H_{14}O$, the molecular weight thereof is 150.3 g/mol, and the structure thereof is shown in Formula 3 below. Carvacrol is a colorless liquid with a unique fragrance, and is well dissolved in ethanol. The biologically active functions of carvacrol, which have been reported to date are antibacterial and anticancer activities, and carvacrol is known to disrupt a bacterial cell wall to inhibit bacterial growth. However, so far, no whitening effect has been reported. In an oral toxicity test for mice, an LD50 value was reported to be 919 mg/kg, and in a transdermal toxicity test for rabbits, an LD50 value is known to be 5,000 mg/kg or more, indicating that carvacrol is relatively safe for the skin.

[44] [Formula 3] Molecular structure of carvacrol

[45] 

[46]

[47] A method of obtaining guaiacol, phytol and carvacrol according to the present invention is not particularly limited, and they may be isolated from natural substances, chemically synthesized using known preparation methods, or commercially available.

[48] In the present invention, the guaiacol, phytol and carvacrol may include guaiacol, phytol and carvacrol hydrates, guaiacol, phytol and carvacrol derivatives, or solvates or stereoisomers thereof within a range of having the same effects as the guaiacol, phytol and carvacrol.

[49] In the present invention, the term "skin whitening" means becoming a skin tone more brightened and an improvement in excessive skin pigmentation such as melasma or freckles, resulting from UV rays, hormones or heredity, by inhibiting the synthesis of a melanin pigment.

[50] The term "cosmetologically acceptable salt," "sitologically acceptable salt," "pharmaceutically acceptable salt" or "salt thereof" used herein is a salt prepared by bonding guaiacol, phytol and carvacrol with a different material, and a material exhibiting similar activities to guaiacol, phytol and carvacrol. The "cosmetologically acceptable salt," "sitologically acceptable salt," "pharmaceutically acceptable salt" or "salt thereof" may be an acid addition salt formed by a free acid. The acid addition salt may be prepared by a conventional method, for example, by dissolving a compound in an excessive amount of acid aqueous solution, and precipitating the salt using a water-miscible organic solvent, for example, methanol, ethanol, acetone or acetonitrile. In addition, equimolar amounts of the compounds and an acid in water or alcohol (e.g., glycol monomethyl ether) may be heated, the mixture may be evaporated or dried, or the precipitated salt may be suction-filtered.

[51] As the free acid, an inorganic acid or organic acid may be used. Non-limiting examples of the inorganic acids may include hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid and tartaric acid, which may be used alone or in combination of two or more thereof. Non-limiting examples of the organic acids may be methanesulfonic acid, p-toluenesulfonic acid, acetic acid, trifluoroacetic acid, maleic acid,

succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, citric acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid and hydroiodic acid, which may be used alone or in combination of two or more thereof.

[52] In addition, the guaiacol, phytol and carvacrol may form a cosmetologically or sitologically acceptable metal salt using a base. An alkali metal or alkaline earth metal salt may be obtained by, for example, dissolving the compounds in an excessive amount of an alkali metal hydroxide or alkaline earth metal hydroxide solution, filtering an undissolved compound salt and then evaporating the filtrate, and drying the evaporated product. The metal salt may be, particularly, a sodium, potassium or calcium salt, but the present invention is not limited thereto. In addition, a silver salt corresponding thereto may be obtained by the reaction of an alkali metal or alkaline earth metal salt with a suitable silver salt (e.g., silver nitrate).

[53] The guaiacol, phytol and carvacrol salts may include, unless indicated otherwise, salts of an acidic or basic group that can be present in the compounds of guaiacol, phytol and carvacrol. For example, the guaiacol, phytol and carvacrol salts may include sodium, calcium and potassium salts of a hydroxyl group, and other cosmetologically acceptable salts of an amino acid may include hydrobromides, sulfates, hydrogen sulfates, phosphates, hydrogen phosphates, dihydrogen phosphates, acetates, succinates, citrates, tartrates, lactates, mandelates, methanesulfonates (mesylates) and p-toleuenesulfonates (tosylates), which may be prepared by a method of preparing a salt known in the art.

[54] The present invention provides a cosmetic composition for skin whitening, which includes guaiacol, phytol and carvacrol, or cosmetologically acceptable salts thereof as active ingredients.

[55] In the cosmetic composition of the present invention, an effective content of the active ingredient may be, but is not particularly limited, 0.0001 to 20 wt% with respect to the total weight of the composition. When the active ingredient is contained at less than 0.0001 wt% in the cosmetic composition, since its content is small, there may be no expected whitening improving effect, and when the active ingredient is contained at more than 20 wt%, the change in effect is insignificant or it is possible to exhibit conventionally known toxicity.

[56] The term "cosmetic composition" used herein is a composition containing the compounds, and is possible to be prepared in any form. A cosmetic prepared using the composition may be prepared in a form of, for example, creams such as a nourishing cream, an eye cream, a massage cream and a cleansing cream, packs, lotions such as a nourishing lotion, essences, toners such as a skin softener and a nourishing toner,

powders, foundations and makeup bases, and to attain the objects of the present invention, a cosmetic may be prepared in any form selected from the above examples, but the present invention is not limited thereto. In addition, the cosmetic composition according to the present invention may be formulated by a conventional method of producing a cosmetic.

[57] Specifically, the cosmetic of the present invention may be prepared in any one form selected from the group consisting of a skin lotion, a skin softener, a skin toner, an astringent, a lotion, a milk lotion, a moisturizing lotion, a nourishing lotion, a massage cream, a nourishing cream, a moisturizing cream, a hand cream, an essence, a pack, a mask pack, a mask sheet, an exfoliate, a soap, a shampoo, a cleansing foam, a cleansing lotion, a cleansing cream, a body lotion, a body cleanser, an emulsion, a pressed powder, a loose powder and an eye shadow.

[58] The cosmetic composition of the present invention may include other additives such as an excipient, a carrier, etc., in addition to active ingredients (guaiacol, phytol and carvacrol, or salts thereof), and it is possible to apply and formulate common ingredients formulated in general skin cosmetics as needed.

[59] Specifically, the cosmetic composition of the present invention may further include a transdermal penetration enhancer. The term "transdermal penetration enhancer" used herein is a composition facilitating the penetration of a desired ingredient into the vascular cells of the skin with a high absorption rate. Preferably, other phospholipids and liposomes used in lecithin cosmetics are included as a transdermal penetration enhancer, but the present invention is not limited thereto.

[60] In addition, as an oil that can be mainly used as an oil-phase ingredient, one or more selected from vegetable oil, mineral oil, silicone oil and synthetic oil may be used. More specifically, mineral oil, cyclomethicone, squalane, octyldodecyl myristate, olive oil, *Vitis vinifera* seed oil, macadamia nut oil, glyceryl octanoate, castor oil, ethyl hexyl isononanoate, dimethicone, cyclopentasiloxane and sunflower seed oil may be used.

[61] In addition, to reinforce an emulsifying ability, a surfactant or higher alcohol may be added at 0.1 to 5 wt%. As the surfactant, a common surfactant such as a non-ionic surfactant, an anionic surfactant, a cationic surfactant, an amphoteric surfactant, or a phospholipid may be used, and specifically, sorbitan sesquinoleate, polysorbate 60, glyceryl stearate, lipophilic glyceryl stearate, sorbitan oleate, sorbitan stearate, DEA-cetylphosphate, sorbitan stearate/sucrose cocoate, glycerylstearate/polyethylene glycol-100 stearate, ceteareth-6 olivate, arachidiylalcohol/vehenylalcohol/arachidyl glycoside, or polypropylene glycol-26-buteth-26/polyethylene glycol-40 hydrogenated castor oil may be used. The higher alcohol may be an alcohol having 12 to 20 carbon atoms, for example, cetyl alcohol, stearyl alcohol, octyldodecanol, or isostearyl alcohol, which may be used alone or in combination of two or more thereof.

[62] To regulate the viscosity or hardness of a water phase, 0.001 to 5 wt% of one or more thickening agents selected from a carbomer, xanthan gum, bentonite, magnesium aluminum silicate, cellulose gum and dextrin palmitate may be further added.

[63] In addition, as needed, the cosmetic composition of the present invention may further include medicinal ingredients such as higher fatty acids and vitamins, and also include a UV blocking agent, an antioxidant (butylhydroxyanisole, propyl gallate, erythorbic acid, tocopherylacetate or butyrated hydroxytoluene), a preservative (methylparaben, butylparaben, propylparaben, phenoxyethanol, imidazolidinylurea or chlorphensin), a colorant, a pH adjuster (triethanolamine, citric acid, sodium citrate, malic acid, sodium malate, fumaric acid, sodium fumarate, succinic acid, sodium succinate, sodium hydroxide or sodium hydrogen phosphate), a moisturizing agent (glycerin, sorbitol, propylene glycol, butylene glycol, hexylene glycol, diglycerin, betain, glycereth-26 or methyl gluceth-20), and a lubricant.

[64] In addition, the cosmetic composition of the present invention may further include a supplementary material that is able to provide an essential nutrient to the skin, and preferably includes a natural flagrance, a cosmetic fragrance or a medical herb, and also include additives which are not limited to the above examples.

[65] In addition, the present invention provides a skin whitening formulation for external use, which includes guaiacol, phytol and carvacrol, or salts thereof as active ingredients.

[66] The term "dermal formulation for external use" is the inclusive concept of all general materials for external use, and non-limiting examples of forms of the dermal formulations for external use include plasters, lotions, liniments, liquids and solutions, aerosols, extracts, ointments, fluid extracts, emulsions, suspensions, capsules, creams, soft or hard gelatin capsules, patches, and sustained-release agents.

[67] The dermal formulation for external use according to the present invention may be a parenteral agent prepared in the form of a solid, semi-solid or liquid by adding a commercially available inorganic or organic carrier, excipient and diluent. The formulation for parenteral administration may be a transdermally-administered form selected from the group consisting of a drop, an ointment, a lotion, a gel, a cream, a patch, a spray, a suspension and an emulsion, but the present invention is not limited thereto.

[68] The carrier, excipient and diluent that can be included in the formulation for external use may include lactose, dextrose, sucrose, oligosaccharides, sorbitol, mannitol, sorbitol, mannitol, xylitol, erythritol, maltitol, starch, acacia gum, alginate, gelatin, calcium phosphate, calcium silicate, cellulose, methyl cellulose, microcrystalline cellulose, polyvinyl pyrrolidone, water, methyl hydroxybenzoate, propylhydroxybenzoate, talc, magnesium stearate and mineral oil

[69] In terms of the form of a composition for the dermal formulation for external use,

other ingredients other than the composition of the present invention may be suitably selected and formulated by those of ordinary skill in the art without difficulty according to the forms or purposes of other formulations for external use, and in this case, when being simultaneously applied with other raw materials, a synergistic effect may occur.

[70] In addition, the present invention provides a health functional food composition for skin whitening, which includes guaiacol, phytol and carvacrol, or sitologically acceptable salts as active ingredients.

[71] The term "health functional food" used herein refers to food manufactured and processed in the form of tablets, capsules, powder, granules, liquids and pills using raw materials or ingredients with useful functionalities for the human body. Here, the "functionality" means the useful effects for health care, such as the control of nutrients or physiological actions in terms of the structure and function of the human body. The health functional food of the present invention can be prepared by a method conventionally used in the art, and during the preparation, raw materials and ingredients, which are generally used in the art, may be added. In addition, the health functional food may be prepared in any form that is recognized as a health functional food without limitation. Unlike generic drugs, since the health functional food composition of the present invention is prepared of edible raw materials, it has no side effects that can occur in long-term use and excellent portability, and thus can be used as a supplement for improving a skin whitening effect.

[72] The health functional food composition according to the present invention may be prepared in any one dosage form selected from the group consisting of a tablet, a granule, a powder, a capsule, a liquid solution and a pill.

[73] The health functional food composition according to the present invention may include guaiacol, phytol and carvacrol as active ingredients, and may be formulated in the form of a powder, a liquid, a tablet, a soft capsule, a granule, a tea bag, an instant tea or a drink. The contents of guaiacol, phytol and carvacrol as active ingredients may be appropriately determined depending on the purpose of use (prevention or improvement). Generally, the amount of the active ingredients (guaiacol, phytol and carvacrol or salts thereof) included in the health functional food composition may be 0.1 to 20 wt% with respect to the total weight of food. However, for health and hygiene or long-term use for health care, the amount may be lower than the above-mentioned range. In addition, the health functional food composition according to the present invention may contain, as well as the active ingredients, other ingredients that can give a synergistic effect to the main effect of the present invention, for example, a skin tone-improving (whitening) compound such as vitamin C, or natural substances such as a green tea extract, a *Broussonetia* extract, a licorice extract, a mulberry root

extract, *Arecae semen* extract, a *Scutellaria baicalensis* root extract, and a *Panax ginseng* extract.

[74] The health functional food composition formulated in the above-described form may be directly added to food or used with another food or food ingredient, and may be appropriately used according to a conventional method. Examples of the food include drinks, meat, sausage, bread, biscuits, rice cakes, chocolate, candy, snacks, sweets, pizza, ramen, other noodles, gums, dairy products including ice creams, all types of soup, beverages, alcoholic beverages and vitamin complexes, dairy products, and all types of health functional food are included in a common sense.

[75] When the health functional food composition of the present invention is a drink, guaiacol, phytol and carvacrol are contained as essential ingredients at the above-mentioned rates, and there is no particular limitation to other ingredients used to prepare a drink. Like common beverages, several flavoring agents or natural carbohydrates may be contained as additional ingredients. Examples of the natural carbohydrate include common saccharides, for example, monosaccharides such as glucose, fructose, etc.; disaccharides such as maltose, sucrose, etc.; and polysaccharides such as dextrin, cyclodextrin, etc., and sugar alcohols such as xylitol, sorbitol, erythritol, etc. Other than those described above, natural flavoring agents and synthetic flavoring agents may be used as flavoring agents. A content of the natural carbohydrate may be approximately 1 to 20 g, and preferably, 5 to 12 g per 100 mL of the composition of the present invention in general.

[76] The health functional food composition of the present invention may contain various nutrients, vitamins, minerals (electrolytes), flavoring agents including synthetic and natural flavoring agents, coloring agents, fillers (cheese, chocolate, etc.), pectic acid and a salt thereof, alginic acid and a salt thereof, organic acids, protective colloidal thickening agents, pH adjusters, stabilizers, preservatives, glycerin, alcohols, or carbonizing agents used in carbonated beverages. In addition, the food composition of the present invention may contain a natural fruit juice, and pulp for manufacturing a fruit juice beverage and vegetable beverage. Such ingredients may be used alone or in combination. The content of such an additive is not significant, but is generally selected within a range of 0.1 to approximately 20 parts by weight with respect to 100 parts by weight of the active ingredients (guaiacol, phytol and carvacrol, or salts thereof).

[77] In addition, the present invention provides a pharmaceutical composition for preventing or treating skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[78] The content of the guaiacol, phytol and carvacrol or salts thereof is preferably 0.0001 to 20 wt% with respect to the total weight of the composition. When the content is more than 20 wt%, an effect change is insignificant, or a conventionally known

toxicity may be exhibited, and when the content is less than 0.0001%, the effect is insignificant.

[79] When the guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof according to the present invention are used in a medicine, one or more of active ingredients exhibiting the same or similar function may be further contained. For example, a known whitening ingredient may be included. When an additional whitening ingredient is included, the skin whitening effect of the composition of the present invention may be further improved. Upon addition of this ingredient, skin safety according to combined use, ease of formulation, and the stability of the active ingredients may be considered. In one embodiment of the present invention, the pharmaceutical composition may further include vitamin C as a whitening ingredient known in the art. The additional skin tone-improving (whitening) ingredient may be included at 0.0001 to 10 wt% with respect to the total weight of the composition, and the content range may be adjusted according to parameters such as an effect of inhibiting tyrosinase activity, skin safety, and ease of formulation of the compounds of Formulas 1 to 3.

[80] The pharmaceutical composition for preventing or treating skin pigmentation according to the present invention may further include a pharmaceutically acceptable carrier.

[81] The pharmaceutically acceptable carrier may contain various ingredients such as a buffer, a sterile water for injection, normal saline or phosphate buffered saline, sucrose, histidine, a salt and a polysorbate.

[82] The pharmaceutical composition of the present invention may be orally or parenterally administered, and may be administered in the forms of generic medicines, for example, various oral and parenteral forms in clinical administration. For preparation, the pharmaceutical composition may be prepared using a diluent or excipient such as a filler, a bulking agent, a binder, a wetting agent, a disintegrant or a surfactant, which is generally used.

[83] A solid formulation for oral administration may be a tablet, pill, powder, granule or capsule, and such a solid formulation may be prepared by adding at least one of excipients, for example, starch, calcium carbonate, sucrose, lactose and gelatin, to the pharmaceutical composition of the present invention.

[84] Other than simple excipients, lubricants such as magnesium stearate, talc, etc. are also used. As a liquid preparation for oral administration, a suspending agent, a liquid for internal use, an emulsion or a syrup is used, and other than a commonly used simple diluent such as water or a liquid paraffin, various excipients, for example, a wetting agent, a sweetening agent, a fragrance and a preservative may be included.

[85]

[86] A formulation for parenteral administration includes a sterilized aqueous solution, a non-aqueous solvent, a suspension, an emulsion, a lyophilizing agent and a suppository. As the non-aqueous solvent or suspension, propylene glycol, polyethylene glycol, a vegetable oil such as olive oil, or an injectable ester such as ethyl oleate may be used. As a suppository base, Witepsol, Tween 61, cacao butter, laurin butter, or glycerogelatin may be used.

[87] The pharmaceutical composition of the present invention may serve to prevent or treat preferable skin pigmentation when including effective amounts of guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof. In the present invention, the "effective amount" refers to an amount of a compound that can inhibit or suppress skin pigmentation, or reducing pigments previously produced. The effective amounts of the guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof, which are included in the composition of the present invention may vary according to a form in which the composition is commercialized, a method of applying the compounds to the skin and the time of staying on the skin. For example, when the composition is commercialized as a medicine for dermatological treatment such as skin pigmentation, compared to when being commercialized as a cosmetic usually applied to the skin, the guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof may be included at high concentrations.

[88] In addition, the present invention provides a quasi-drug composition for preventing or improving skin pigmentation, which includes guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[89] The term "quasi-drug" means products that are less effective than medicines among products used to diagnose, treat, improve, alleviate, treat or prevent a human or animal disease, and for example, according to the pharmacist law, the quasi-drugs include products used for the treatment or prevention of a human/animal disease, and products that have a slight effect on or do not directly act on the human body, except products used as medicines.

[90] The quasi-drug composition is used to prevent or improve skin pigmentation, and its form is not particularly limited. For example, the quasi-drug composition may be a cosmetic composition prepared in the form of a skin softener, a nourishing toner, a massage cream, a nourishing cream, a pack, a mask pack, a mask sheet, a gel or a skin adhesive-type cosmetic, or a transdermal form such as a lotion, an ointment, a gel, a cream, a patch or a spray.

[91] In addition, for any form, the quasi-drug composition may be formulated by randomly selecting other ingredients according to the form or purpose of a quasi-drug. A mixed amount of the active ingredients may be suitably determined according to the purpose of use (inhibition or alleviation). For example, conventional adjuvants and

carriers such as a thickening agent, a stabilizer, a solubilizer, vitamins, pigments and flavors.

[92] The content of the guaiacol, phytol and carvacrol, or salts thereof of the present invention are preferably 0.0001 to 20 wt% based on the total weight of the quasi-drug composition. When the content is more than 20 wt%, color and stability may be degraded in the preparation of the composition, and when the content is less than 0.0001%, the effect of the active ingredients is insignificant.

[93] In addition, for each form of quasi-drug composition, other ingredients, except the essential ingredients, may be appropriately selected and formulated by those of ordinary skill in the art without difficulty according to a form or purpose of use.

[94] Hereinafter, the present invention will be described in further detail with reference to examples. The examples are merely provided to more fully describe the present invention, and it will be obvious to those of ordinary skill in the art that the scope of the present invention is not limited to the following examples.

[95]

[96] ***Example: Evaluation of melanogenesis inhibitory effect of guaiacol, phytol and carvacrol using B6F10 melanocytes***

[97] **1-1. Experimental method**

[98] **1) Experimental materials and cell culture**

[99] All of α-MSH, guaiacol, phytol and carvacrol used in the experiment were purchased from Sigma Aldrich. B16F10 melanocytes were purchased from ATCC (Manassas, VA, USA), and the purchased cells were incubated using 10% fetal bovine serum (FBS)-containing DMEM in a 5% CO_2 incubator at 37 ℃.

[100]

[101] **2) Measurement of production amount of melanin in cells**

[102] $1X10^5$ cells/well of B6F10 melanocytes were incubated in 10% FBS-containing DMEM at 37 ℃ in 5% CO_2, dispensed into a 6-well plate such that the cells were grown to a confluency of 80% or more. Normal cells are cells not treated with α-MSH inducing melanogenesis, and control cells were designed as cells treated with α-MSH (100 nM). The cells incubated under the above-mentioned conditions were treated with a composite composition consisting of guaiacol (20 μM)-phytol (10 μM)-carvacrol (20 μM) as well as α-MSH (100 nM), followed by culturing for 48 hours. In addition, even when guaiacol, phytol or carvacrol was used alone, cells to be confirmed as having a melanogenesis inhibitory effect were treated with α-MSH (100 nM)+guaiacol (20 μM), α-MSH (100 nM)+phytol (10 μM) or α-MSH (100 nM)+carvacrol (20 μM) and incubated under the same conditions as mentioned above.

[103] Afterward, the cells were washed with PBS twice and then collected. The collected cells were centrifuged at 1,000 rpm for 5 minutes, and a pellet color was observed with

the naked eye. The cell pellets were suspended in 200 μL of a 10% DMSO-added 1N NaOH solution, and absorbance was measured using a microplate reader at 400 nm. An intracellular melanin content was calculated by calibrating the amount of protein in the absorbance value.

[104]

[105] **3) RNA extraction and PCR analysis**

[106] Total RNA was extracted from cells using TRIzol, and the extracted RNA sample was subjected to reverse transcription using oligo dT primers and superscript reverse transcriptase (GIBCO BRL, Gaithersburg, MD, USA) to synthesize cDNA. cDNA obtained by reverse transcription was used as a template, the 5' and 3' flanking sequences of cDNA of a gene to be amplified were used as primers, and quantitative PCR was performed using iQ SYBR Green Supermix (Bio-Rad) and CFX Connect™ Real-Time PCR Detection System (Bio- Rad). The primer sequences used herein are shown in Table 1.

[107] [Table 1]

[108] Primer sequences used in PCR

[109]

Gene description	Primer	Sequence (5'→3')	Annealing	PCR product
Tyrosinase	F	CTCTGGGCTTAGCAGTAGGC (SEQ ID NO: 1)	55	164
	R	GCAAGCTGTGGTAGTCGTCT (SEQ ID NO: 2)		
microphthalmia transcription factor (MITF)	F	AGCGTGTATTTTCCCCACAG (SEQ ID NO: 3)	55	103
	R	TAGCTCCTTAATGCGGTCGT (SEQ ID NO: 4)		
Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)	F	CAAAATGGTGAAGGTCGGTG (SEQ ID NO: 5)	55	104
	R	TTTGCCGTGAGTGGAGTCAT (SEQ ID NO: 6)		

[110] **1-2. Experimental results**

[111] **1) Melanogenesis inhibitory effect of guaiacol, phytol and carvacrol in B6F10 melanocytes**

[112] Synthesis was initiated in melanosomes, which are cell organelles in melanocytes, and when the melanocytes were activated by the exposure to UV rays, melanin was produced through a series of enzymatic reactions.

[113] B6F10 melanocytes were treated with a composite composition consisting of guaiacol-phytol-carvacrol in addition to α-MSH, incubated at 37 ℃ under 5% CO_2 for

48 hours, and then collected. In addition, it was investigated whether a melanogenesis inhibitory effect was also exhibited in cells treated with a single composition. A melanin content was measured using the cell lysate obtained above.

[114] As a result, compared with normal cells not treated with α-MSH, the melanin content in control cells treated with α-MSH significantly increased, for example, by 134%. Meanwhile, it was confirmed that, in the cells treated with the guaiacol-phytol-carvacrol composite composition as well as α-MSH, compared with the control cells, the melanin content significantly decreased 33%, there was no change in melanin content in cells treated with only one of guaiacol, phytol and carvacrol as well as α-MSH, compared with α-MSH-treated control cells (FIG. 1).

[115] As a result of visually observing the pellet color of the B6F10 melanocyte, compared with pellets of normal cells not treated with α-MSH, it was confirmed that pellets of the α-MSH-treated control cells turned black. It was confirmed that, compared with those of the control cells, the color of the pellets of the cells treated with the guaiacol-phytol-carvacrol composite composition as well as α-MSH became significantly lighter. Meanwhile, it was confirmed that there was no change in the color of cells treated with only one of guaiacol, phytol and carvacrol as well as α-MSH, compared with the control cells (FIG. 2). Therefore, it can be confirmed that the melanogenesis inhibitory effect of the guaiacol-phytol-carvacrol composite composition is most excellent.

[116] **2) Confirmation of inhibition of melanogenesis by change in gene expression in B6F10 melanocytes**

[117] Tyrosinase is well known for acting in the early stage of melanogenesis to regulate a rate of the melanogenesis, and MITF is well known for inducing enzyme expression by binding to E-box (CATGTG) present in a gene promotor of tyrosinase.

[118] PCR analysis was performed on B6F10 melanocytes to investigate whether the melanogenesis inhibitory effect of the guaiacol-phytol-carvacrol composite composition is associated with the inhibition of the expression of an enzyme such as tyrosinase and the regulation of the expression of a transcription factor, MITF. As a result, it was confirmed that the expression of MITF and tyrosinase significantly increases in the α-MSH-treated control cells, compared with normal cells (basal), and compared to the control cells, in the cells treated with the guaiacol-phytol-carvacrol composite composition as well as α-MSH, the expression of MITF and tyrosinase significantly decreases by 39% and 34% (FIG. 3).

Mode for the Invention

[119] **[Preparation Example 1] Production of cosmetics**

[120] 1-1. Production of skin softener

[121] A skin softener containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 2 below.

[122] [Table 2]

[123]

Component	Preparation Example 1-1 (wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.1
Ethanol	10.0
Polylauric acid, polyoxyethylene sorbitan	1.0
p-hydroxybenzoic acid	0.2
Glycerin	5.0
1,3-butylene glycol	6.0
Fragrance	q.s.
Pigment	q.s.

[124] 1-2. Production of nourishing toner

[125] A nourishing toner containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 3 below.

[126] [Table 3]

[127]

Component	Preparation Example 1-2(wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.05
Vaseline	2.0
Sorbitan sesquioleate	0.8
Polyoxyethylene oleyl ether	1.2
p-hydroxybenzoic acid	q.s.
Propylene glycol	5.0
Ethanol	3.2
Carboxyvinyl polymer	18.0
Potassium hydroxide	0.1
Pigment	q.s.
Fragrance	q.s.

[128] 1-3. Production of nourishing cream

[129] A nourishing cream containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 4 below.

[130] [Table 4]

[131]

Component	Preparation Example 1-3(wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.2
Stearic acid	15.0
Cetanol	1.0
Potassium hydroxide	0.7
Glycerin	5.0
Propylene glycol	3.0
Preservative	q.s.
Fragrance	q.s.
Distilled water	to 100

[132] 1-4. Production of pack

[133] A pack containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 5 below.

[134] [Table 5]

[135]

Component	Preparation Example 1-4(wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.05
Glycerin	5.0
Propylene glycol	4.0
Polyvinyl alcohol	15.0
Ethanol	8.0
Polypxyethylene oleyl ether	1.0
p-hydroxybenzoic acid	0.2
Pigment	q.s.
Fragrance	q.s.

[136] 1-5. Production of essence

[137] An essence containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 6 below.

[138] [Table 6]

[139]

Component	Preparation Example 1-5(wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.2
Propylene glycol	10.0
Glycerin	10.0
Sodium hyaluronate solution (1%)	5.0
Ethanol	5.0
Polyoxyethylene hydrogenated castor oil	1.0
p-hydroxybenzoic acid	0.1
Fragrance	q.s.
Distilled water	to 100

[140] **[Preparation Example 2] Production of health functional food**

[141] 2-1. Production of health functional food

[142] A health functional food containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 7 below.

[143] [Table 7]

[144]

Component	Preparation Example 2-1
guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	1000 mg
Vitamin mixture	q.s.
Vitamin A acetate	1.0 mg
Vitamin E	0.13 mg
Vitamin B1	0.15 mg
Vitamin B2	0.5 mg
Vitamin B6	0.2 μg
Vitamin B12	10 mg
Vitamin C	10 μg
Biotin	1.7 mg
Nicotinic acid amide	50 μg
Folic acid	0.5 mg
Calcium pantothenate	q.s.
Inorganic mixture	q.s.
Ferrous sulfate	1.75 mg
Zinc oxide	0.82 mg
Magnesium carbonate	25.3 mg
Potassium phosphate, monobasic	15 mg
Potassium phosphate, dibasic	55 mg
Potassium citrate	90 mg
Calcium carbonate	100 mg
Magnesium chloride	24.8 mg

[145] While ingredients relatively suitable for the health functional food were formulated according to an exemplary embodiment, the ratios of the vitamins and the mineral mixture may vary arbitrarily, and the above-mentioned ingredients were mixed according to a conventional method of producing a health functional food, thereby producing granules, and then the granules were able to be used in the preparation of a health functional food composition according to a conventional method.

[146] 2-2. Production of health beverage

[147] A health beverage containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 8 below.

[148] [Table 8]

[149]

Component	Preparation Example 2-2(mg)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	1000 mg
Citric acid	1000 mg
Oligosaccharides	100 g
Plum concentrate	2 g
Taurine	1 g
Distilled water	q.s.

[150] The ingredients were mixed according to a conventional method of producing a health beverage and heated at 85 °C for approximately 1 hour while stirring. The resulting solution was filtered and collected in a sterile 2L container, sealed and sterilized, and then freeze-stored, followed by the use in the preparation of a health beverage composition of the present invention. While the ingredients relatively suitable for a favorite beverage were mixed according to an exemplary embodiment, the composition ratios may vary arbitrarily according to regional and national preferences such as demand class and nation, and usage.

[151] 2-3. Production of tablet

[152] A tablet containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 9 below.

[153] [Table 9]

[154]

Component	Preparation Example 2-3(mg)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	100 mg
Corn starch	100 mg
Lactose	100 mg
Magnesium stearate	2 mg

[155] 2-4. Production of capsule

[156] A capsule containing guaiacol, phytol and carvacrol was produced according to a conventional method of producing a capsule with the composition shown in Table 10 below.

[157] [Table 10]

[158]

Component	Preparation Example 2-4(mg)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	100 mg
Corn starch	100 mg
Lactose	100 mg
Magnesium stearate	2 mg

[159] 2-5. Production of pill

[160] A pill was produced to be 4 g per pill according to a conventional method of

producing a pill with the composition shown in Table 11 below.

[161] [Table 11]

[162]

Component	Preparation Example 2-5(mg)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	1 g
Lactose	1.5 g
Glycerin	1 g
Xylitol	0.5 g

[163] 2-6. Production of granule

[164] A granule was produced by drying ingredients at 60 °C into granules by adding 100 mM of 30% ethanol and then filling a pouch with the granules.

[165] [Table 12]

[166]

Component	Preparation Example 2-6(mg)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	150 mg
Soybean extract	50 mg
Glucose	200 mg
Starch	600 mg

[167] [Preparation Example 3]

[168] Production of dermal ointment for external use

[169] A dermal ointment for external use containing guaiacol, phytol and carvacrol was produced with the composition shown in Table 13 below.

[170] [Table 13]

[171]

Component	Preparation Example 3(wt%)
Guaiacol, phytol and carvacrol (weight ratio - 1:0.5:1)	0.5
Diethyl sebacate	8.0
Spermaceti	5.0
Polyoxyethylene oleyl ether phosphate	6.0
Sodium benzoate	q.s.

[172] A composition according to the present invention, which includes guaiacol, phytol and carvacrol as active ingredients, has an excellent effect of inhibiting melanogenesis induced by αMSH, is safe for the human body and has few side effects, and thus can be widely used as materials for cosmetics, health functional food, medicines or quasi-drugs.

[173] It will be apparent to those skilled in the art that various modifications can be made to the above-described exemplary embodiments of the present invention without

departing from the spirit or scope of the invention. Thus, it is intended that the present invention covers all such modifications provided they come within the scope of the appended claims and their equivalents.

[174]

Claims

[Claim 1] A cosmetic composition for skin whitening, comprising guaiacol, phytol and carvacrol, or cosmetologically acceptable salts thereof as active ingredients.

[Claim 2] The cosmetic composition of claim 1, wherein the active ingredients inhibit the expression of a microphthalmia transcription factor (MITF) or tyrosinase.

[Claim 3] The cosmetic composition of claim 1, wherein the active ingredients inhibit melanogenesis induced by melanocyte-stimulating hormone (α-MSH).

[Claim 4] The cosmetic composition of claim 1, wherein the composition is prepared in any one form selected from the group consisting of a skin lotion, a skin softener, a skin toner, an astringent, a lotion, a milk lotion, a moisturizing lotion, a nourishing lotion, a massage cream, a nourishing cream, a moisturizing cream, a hand cream, an essence, a pack, a mask pack, a mask sheet, an exfoliate, a soap, a shampoo, a cleansing foam, a cleansing lotion, a cleansing cream, a body lotion, a body cleanser, an emulsion, a pressed powder, a loose powder and an eye shadow.

[Claim 5] The cosmetic composition of claim 1, wherein the active ingredients are contained at 0.0001 to 20 wt% with respect to the total weight of the cosmetic composition.

[Claim 6] The cosmetic composition of claim 1, wherein the composition contains 20 to 200 parts by weight of phytol and 20 to 200 parts by weight of carvacrol with respect to 100 parts by weight of guaiacol.

[Claim 7] A skin whitening formulation for external use, comprising guaiacol, phytol and carvacrol, or salts thereof as active ingredients.

[Claim 8] A health functional food composition for skin whitening, comprising guaiacol, phytol and carvacrol, or sitologically acceptable salts thereof as active ingredients.

[Claim 9] The health functional food composition of claim 8, wherein the composition is prepared in any one dosage form selected from the group consisting of a tablet, a granule, a powder, a capsule, a liquid solution and a pill.

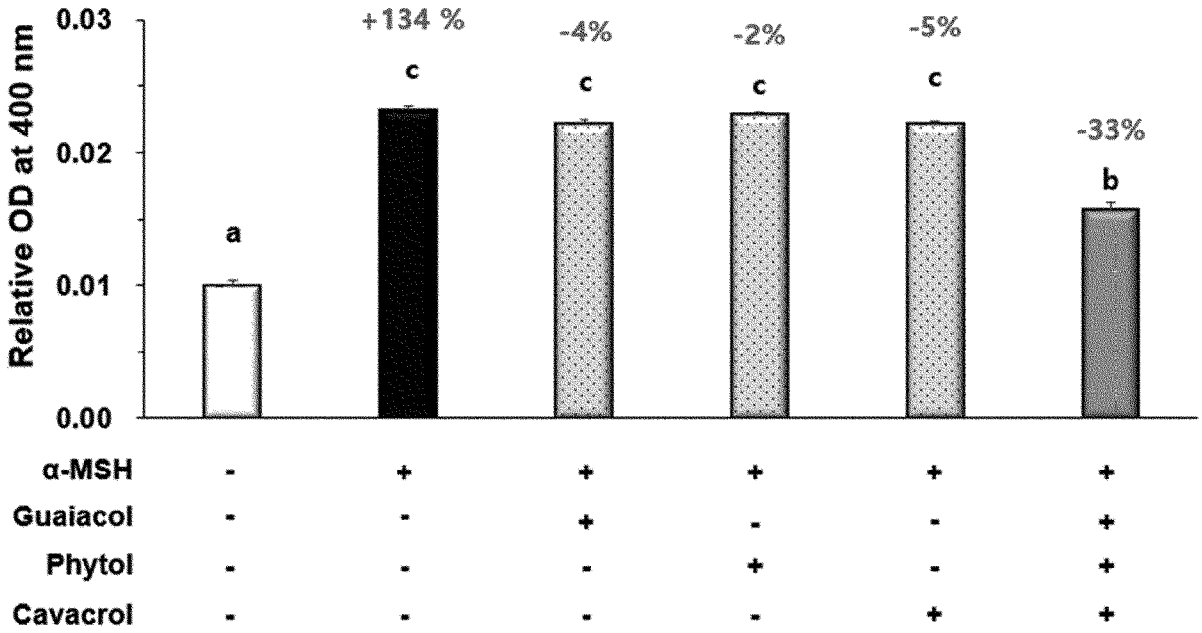
[Claim 10] A pharmaceutical composition for preventing or treating skin pigmentation, comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

[Claim 11] A quasi-drug composition for preventing or improving skin pigmentation, comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

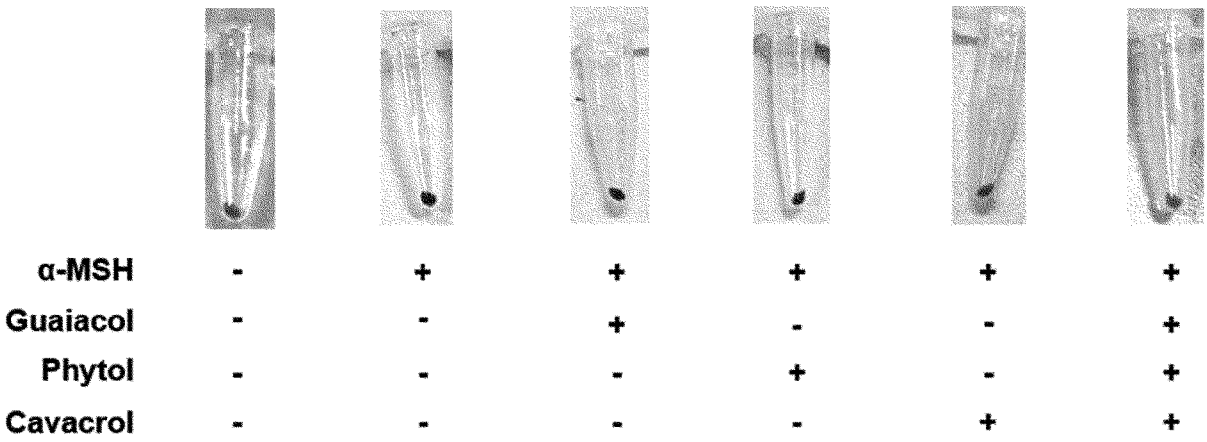
[Claim 12] A method for preventing or treating skin pigmentation, the method comprising administering a composition comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients, or allowing it to be taken, to a subject.

[Claim 13] A use of a composition for preventing or treating skin pigmentation, the composition comprising guaiacol, phytol and carvacrol, or pharmaceutically acceptable salts thereof as active ingredients.

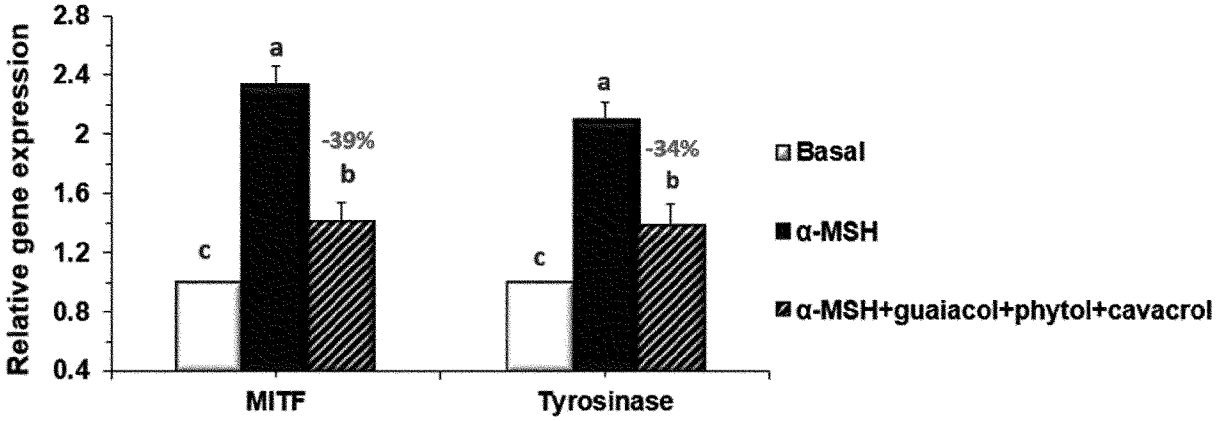
[Fig. 1]



[Fig. 2]



[Fig. 3]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2020/004040

A. CLASSIFICATION OF SUBJECT MATTER

A61K 8/34(2006.01)i, A61Q 19/02(2006.01)i, A23L 33/105(2016.01)i, A61K 31/085(2006.01)i, A61K 31/045(2006.01)i, A61K 31/05(2006.01)i, A61P 17/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 8/34; A23L 33/105; A61K 7/00; A61K 7/48; A61Q 19/02; C07C 43/23; A61K 31/085; A61K 31/045; A61K 31/05; A61P 17/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: skin whitening, guaiacol, phytol, carvacrol

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 09-249544 A (SNOW BRAND MILK PROD CO., LTD.) 22 September 1997 See paragraphs [0004], [0009], [0013]; and claim 1.	1-11,13
Y	JP 2014-073969 A (MARUZEN PHARMACEUT CO., LTD.) 24 April 2014 See paragraphs [0018], [0030], [0033]; and claims 1-4.	1-11,13
Y	JP 11-029516 A (SHISEIDO CO., LTD.) 02 February 1999 See paragraphs [0053], [0064], [0080]; and claims 1-3.	1-11,13
A	SATOOKA, HIROKI, "Naturally occurring melanin synthesis regulators and their modes of action." University of California, Berkeley, 2011 See pages 4, 34; and figure 6.	1-11,13
PX	KR 10-2089209 B1 (INDUSTRY-ACADEMIC COOPERATION FOUNDATION, YONSEI UNIVERSITY) 13 March 2020 See the whole document.	1-11,13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2020 (18.06.2020)	**19 June 2020 (19.06.2020)**

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2020/004040

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 12 pertains to a method for treatment of the human body by surgery or therapy, as well as a diagnostic method (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2020/004040

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 09-249544 A	22/09/1997	None	
JP 2014-073969 A	24/04/2014	JP 5844240 B2	13/01/2016
JP 11-029516 A	02/02/1999	None	
KR 10-2089209 B1	13/03/2020	None	