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(57) Abstract: The present invention provides an antioxidant composition having a superior antioxidative effect: an antioxidant composition comprising oxidized glutathione.
ANTIOXIDANT COMPOSITION COMPRISING OXIDIZED GLUTATHIONE

Technical Field
The present invention relates to antioxidant composition which is characterized by comprising oxidized glutathione.

Background Art
In the prior art, vitamin C, vitamin E, reduced coenzyme Q10 and carotenoids have been most widely employed as anti-oxidants (Patent documents 1 to 5), the development of the anti-oxidants having a superior antioxidative effect has been desired.

Glutathione is a substance known for its superior antioxidative activities. The substance itself is generally an odorless powder. However, an unpleasant odor like sulfur may be developed due to the influence of heat, oxygen, light and the like during preservation in the form of a powder or a preparation containing glutathione as a main component, i.e., a glutathione preparation. In some cases, glutathione content in the preparation is lowered; consequently, the quality of glutathione is deteriorated.


Disclosure of the Invention

Problems to Be Solved by the Invention
An object of the present invention is to provide antioxidant composition having a superior antioxidative effect.

Means for Solving the Problems
The present invention relates to the following.

[1] An antioxidant composition comprising oxidized glutathione

[2] The composition of above-mentioned [1], wherein the composition is a cosmetic composition.
Effect of the Invention

According to the present invention, an antioxidant composition available for various use can be provided, since oxidized glutathione has antioxidative activity same as glutathione, has high stability, and does not develop unpleasant odor.

Best Mode for Carrying out the Invention

Antioxidant composition of the present invention is characterized by comprising oxidized glutathione. Oxidized glutathione refers to a glutathione dipeptide in which two molecules of a tripeptide having the gamma-L-Glu-L-Cys-Gly structure (reduced glutathione) are linked by an SS bond to form dimer structure. The oxidized glutathione used in the present invention may be obtained by any production process. Example of the process for the production of oxidized glutathione includes, but not particularly limited to, the method of Acta Biochim. Pol., 17, 175 (1970). Oxidized glutathione can also be purchased from the goods on the market.

Oxidized glutathione of the present invention is preferably isolated or purified. The term "isolated or purified" are used herein mean that a compound (e.g., oxidized glutathione) is separated from natural environment and does not include a part or all of other natural ingredients. Isolated or purified compound does not include other natural ingredients more than at least 60 % by weight, preferably 75 % or more by weight, more preferably 90 % or more by weight. In other words, preferably, isolated or purified oxidized glutathione is added in the antioxidant composition of the present invention.

The antioxidant composition of the present invention may contain, besides oxidized glutathione, appropriate amounts of components (base, carrier, additive etc.) generally used for drug, quasi-drug, food and drink, cosmetic and the like,
according to the use and dosage form of the antioxidant composition.

The components that can be appropriately added are not particularly limited and include, for example, vitamins, amino acids, alcohols, polyvalent alcohols, saccharides, polymer compounds such as gum substances and polysaccharides, surfactants, antiseptic, antibacterial, bacteriocidal agents, pH adjusters, chelating agents, antioxidants, enzyme components, binders, disintegrants, lubricants, fluidizers, algefacients, taste/odor correctives, coating agents, minerals, cellular stimulants, revitalizers, excipients, viscosity-imparting agents, stabilizers, preservatives, isotonicity agents, dispersing agents, adsorbents, disintegration aids, wetting agents or moistening regulators, moisture-proof agents, colorants, flavoring agents or flavors, aromatics, reducing agents, solubilizers, solubilizing agents, bubbling agents, thickeners or viscosity agents, solvents, bases, emulsifiers, plasticizers, buffering agents, gloss agents, fats and oils, moisturizing agents, UV absorbers, irritation reducing agents and the like.

Although the ingredient which can be arbitrarily blended with below is illustrated concretely, it is not limited to these ingredients.

Examples of the vitamins include vitamin A, B, C, D, E, K, folic acid, pantothenic acid, nicotinamide, carnitine, choline, inositol, biotin, and the like.

Examples of the amino acids include leucine, isoleucine, valine, methionine, threonine, alanine, phenylalanine, tryptophan, lysine, glycine, asparagine, aspartic acid, serine, glutamine, proline, tyrosine, cystein, histidine, ornithine, hydroxyproline, hydroxylsine, glycylglycine, aminoethylsulfonic acid, and food hygienically, pharmacologically or cosmetically acceptable salt thereof, and the like.

Examples of the alcohols include ethanol, isopropanol,
lauryl alcohol, cetanol, stearyl alcohol, oleyl alcohol, lanolin alcohol, behenyl alcohol, 2-hexyldecanol, isostearyl alcohol, 2-octyldodecanol, and the like.

Examples of the polyvalent alcohols include ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, polypropylene glycol, 1,3-butylene glycol, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, polyethylene glycol, glycerin, pentaerythritol, sorbitol, mannitol, xylitol, inositol, and the like.

Examples of the saccharides include glucose, fructose, galactose, mannose, ribose, arabinose, xylose, deoxyribose, maltose, trehalose, sucrose, lactose, lactulose, raffinose, maltitol, erythritol, mannitol, xylitol, sorbitol, refined sugar, and the like. These saccharides also include the derivative thereof, for example, phosphates (for example, glucose 6-phosphate etc.) and oxidants (for example, galacturonic acid, glucuronic acid, mannuronic acid, etc.), and food hygienically, pharmacologically or cosmetically acceptable salt thereof, and the like.

Examples of the polymer compounds such as gum substances and polysaccharides, include gum arabic, karaya gum, xanthan gum, carob gum, guar gum, quaiac resin, quince seed, dull man gum, tragacanth, benzoin rubber, locust bean gum, casein, agar, alginic acid, dextrin, dextran, galaginan, gelatin, collagen, pectin, starch, cornstarch, polygalacturonic acid, chitin and its derivative, chitosan and its derivative, elastin, heparin, heparinoid, heparin sulfate, heparan sulfate, hyaluronic acid, chondroitin sulfate, ceramide, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropylcellulose, carboxymethyl cellulose, carboxyethyl cellulose, cellulose, nitrocellulose, polyvinyl alcohol (completely or partially saponified products), polyvinyl pyrrolidone, polyvinyl methacrylate, polyacrylic acid, carboxyvinyl polymer,
polyethyleneimine, ribonucleic acid, deoxyribonucleic acid, and food hygienically, pharmacologically or cosmetically acceptable salt thereof, and the like.

Examples of the surfactants include polyoxyethylene, polyalkyl siloxane, sorbitan monooleate, sorbitan trioleate, sorbitan monostearate, sorbitan monoisostearate, sorbitan monolaurate, sorbitan monopalmitate, sorbitan sesquioleate, diglycerol sorbitan tetra-2-ethylhexylate, diglycerol sorbitan penta-2-ethylhexylate, glycerol mono-cotton seed oil fatty acid ester, glycerol monoeruate, glycerol sesquioleate, glyceryl monostearate, glyceryl monostearate malate, glycerol a,a'-oleate pyroglutamate, propylene glycol monostearate, hydrogenated castor oil derivative, glycerin alkyl ether, polyoxyethylene monooleate, polyoxyethylene distearate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan tetraoleate, polyoxyethylene sorbitol monooleate, polyoxyethylene sorbitol laurate, polyoxyethylene sorbitol pentaoleate, polyoxyethylene sorbitol monostearate, polyoxyethylene sorbitol yellow beeswax, polyoxyethylene glycerol monostearate, polyoxyethylene glycerin monoisostearate, polyoxyethylene glycerin triisostearate, polyoxyethylene lauryl ether, polyoxyethylene oleylether, polyoxyethylene stearylether, polyoxyethylene behenylether, polyoxyethylene cholesterol ether, polyoxyethylene octylphenyl ether, polyoxyethylene nonylphenyl ether, polyoxyethylene dinonylphenyl ether, polyoxyethylene (105) polyoxypropylene (5) glycol, polyoxyethylene (120) polyoxypropylene (40) glycol, polyoxyethylene (160) polyoxypropylene (30) glycol, polyoxyethylene (42) polyoxypropylene (67) glycol, polyoxyethylene (196) polyoxypropylene (67) glycol, polyoxyethylene (20) polyoxypropylene (20) glycol, polyoxyethylene (1) polyoxypropylene (1) cetyl ether, polyoxyethylene (10) polyoxypropylene (4) cetyl ether, polyoxyethylene (17) polyoxypropylene (23) cetyl ether, polyoxyethylene (20)
polyoxypropylene (1) cetyl ether, polyoxyethylene
polyoxypropylene monobutyl ether, polyoxyethylene
polyoxypropylene hydrogenated lanolin, polyoxyethylene
polyoxypropylene glycerin ether, polyoxyethylene castor oil,
5 polyoxyethylene hydrogenated castor oil; anionic form
surfactants such as polyoxyethylene hydrogenated castor oil
hydrogenated monoisoestrate, polyoxyethylene hydrogenated castor oil
triisoestrate, polyoxyethylene hydrogenated castor oil
monopyroglutamate isoestrate diester, polyoxyethylene
hydrogenated castor oil malate, lauric acid monoethanolamide,
10 palm-oil-fatty-acid diethanolamide, fatty acid isopropanol
amide, alkyl carboxylate, alkyl sulfonate, alkylbenzene sulfonates; alkyl phosphonate, alkylamine salt, alkyl
quarternary ammonium salt, alkyl pyridinium salt,
15 polyoxyethylene propylene glycol fatty acid ester,
polyoxyethylene fatty acid amide, sucrose fatty acid ester,
polyoxyethylene nonylphenyl formaldehyde condensate, alkyl
ethoxy dimethylamine oxide, trialkyl phosphate, sodium lauryl
sulfate, soybean lecithin, polysorbate 80, and food
20 hygienically, pharmacologically or cosmetically acceptable
salt thereof, and the like.
Examples of the antiseptic, antibacterial, bacteriocidal
agents include methyl parahydroxybenzoate, ethyl para-
hydroxybenzoate, propyl parahydroxybenzoate, butyl
25 parahydroxybenzoate, acrinol, benzalkonium chloride,
benzethonium chloride, cetylpyridinium chloride, bromination
cetyl pyridinium bromide, chlorhexidine, polyhexamethylene
diguanide, alkylpolyamino ethylglycine, benzyl alcohol,
20 phenethyl alcohol, chlorobutanol, isopropanol, ethanol,
30 phenoxyethanol, sulfur, mercuriochrome, thimerosal, povidone
iodine, dehydroacetic acid, chloroxylenol, cresol, chlorophen,
phenol, resorcinol, orthophenylphenol, isopropylmethyl phenol,
35 hinokitiol, sulfamine, lysozyme, lactoferrin, triclosan, 8-
hydroxyquinoline, undecylenic acid, propionic acid, benzoic
acid, sorbic acid, triclocarban, hydrogen peroxide,
orthophthalaldehyde, and food hygienically, pharmacologically
or cosmetically acceptable salt thereof, and the like.

Examples of the pH adjusters include hydrogen chloride,
sulfuric acid, lactic acid, acetic acid, citric acid, tartaric
acid, malic acid, succinic acid, oxalic acid, gluconic acid,
fumaric acid, propionic acid, acetic acid, aspartic acid,
epsilon aminocaproic acid, glutamic acid, aminomethyl sulfonic
acid, phosphoric acid, polyphosphoric acid, boric acid,
glucono lactone, ammonium acetate, sodium bicarbonate, sodium
carbonate, potassium hydroxide, sodium hydroxide, calcium
hydroxide, magnesium hydroxide, monoethanolamine,
triethanolamine, diisopropanolamine, triisopropanolamine,
lysine, borax, and food hygienically, pharmacologically or
cosmetically acceptable salt thereof, and the like.

Examples of the chelating agents include edetic acid,
citrate, polyphosphoric acid, metaphosphoric acid, ascorbic
acid, succinic acid, phytic acid, 1-hydroxyethane-1,1-
diphosphonic acid, and food hygienically, pharmacologically or
cosmetically acceptable salt thereof, and the like.

Examples of the antioxidants include ascorbic acid and
its derivative, erythorbic acid and its derivative, tocopherol
and its derivative; catechins such as carotene, lycopene,
propyl gallate, tannic acid, epigallocatechin; polyphenol such
as anthocyanine, butylhydroxytoluene, butylhydroxyanisole, p-
hydroxyanisole, and food hygienically, pharmacologically or
cosmetically acceptable salt thereof, and the like.

Examples of the enzyme components include lipase,
amylase, endopeptidase, catalase, lysozyme, Superoxide
dismutase, glutathione peroxidase, elastase, collagenase,
gelatinase, chymotrypsin, and the like.

Examples of the binders include starch, dextrin, gummi
arabicum pulveratum, gelatin, hydroxypropyl starch,
methylcellulose, carboxymethylcellulose sodium,
hydroxypropylcellulose, crystalline cellulose, ethyl cellulose,
polyvinyl alcohol, polyvinyl ether, polyvinyl pyrrolidone,
macrogol, tragacanth, hydroxypropyl methylcellulose, calcium citrate, dextrin, pectin, and the like.

Examples of the disintegrants include starch, hydroxypropyl starch, carboxymethyl cellulose sodium, carboxymethyl cellulose calcium, carboxymethyl cellulose, low-substituted hydroxypropyl cellulose, crystalline cellulose, and the like.

Examples of lubricants include talc, wax, hydrogenated vegetable oil, sucrose fatty acid ester, magnesium stearate, calcium stearate, aluminum stearate, polyethylene glycol, silica, and the like.

Examples of the fluidizers include light anhydrous silicic acid, dried aluminium hydroxide gel, synthetic aluminum silicate, magnesium silicate, and the like.

Examples of the algefacients include essential oil or essential oil constituent such as l-menthol, d-menthol, dl-menthol, d-camphor, dl-camphor, d-borneol, dl-borneol, geraniol, eucalyptus oil, bergamot oil, fennel oil, mentha oil, cinnamon oil, rose oil, peppermint oil, and the like.

Examples of the taste/odor correctives or the coating agents include cacao powder, cinnamom powder, green tea powder, lactose, refined sugar, glucose, mannitol, menthol, camphor, borneol, geraniol, eucalyptus oil, bergamot oil, fennel oil, mentha oil, cinnamon oil, rose oil, peppermint oil, mannitol, xylitol, fragrance essential oil, and the like.

Though the amount of oxidized glutathione in the antioxidant composition of the present invention may be decided appropriately in purpose of use or its preparation, the amount of oxidized glutathione is generally 0.0001-100 % by weight, preferably 0.001-99 % by weight of the antioxidant composition.

The antioxidant composition of the present invention can be applied to drug, quasi-drug, food or beverage, cosmetic composition and like (hereinafter abbreviated as the drug, quasi-drug, food or beverage, and cosmetic composition of the
present invention respectively), since the oxidized glutathione has high stability, and does not develop unpleasant odor.

The dosage form of the drug of the present invention is not particularly limited to and may be oral or non-oral preparation. Oral preparations include tablets (including sublingual tablet, intraoral collapse tablet), capsules (including soft capsule, microcapsule, enteric capsule), granules, powders, lozenges, syrup, emulsion, suspension, and the like, and non-oral preparations include external preparations (e.g., transdermal preparation, ointment and the like), injections (e.g., hypodermic injection, intravenous injection, intramuscular injection, intraperitoneal injection, infusion and the like), bougies (e.g., rectal bougie, vagina bougie and the like).

The drug of the present invention can be prepared by any well known method in a technical field of the pharmaceutics by mixing oxidized glutathione and a pharmacologically acceptable carrier appropriately.

Examples of pharmacologically acceptable carriers include excipients (e.g., saccharides such as lactose, refined sugar, glucose, sucrose, mannitol, sorbitol and the like; starches of potato, wheat, corn, and the like; inorganic substances such as calcium carbonate, calcium sulfate, calcium phosphate, sodium hydrogen carbonate, sodium chloride, and the like; powders of plants such as licorice, gentian and the like), binders (e.g., polyvinyl alcohol, hydroxypropyl cellulose, methylcellulose, ethylcellulose, carmellose, starch paste liquid and the like), disintegrators (e.g., starch, agar, gelatine powder, microcrystallite cellulose, carmellose sodium, carmellose calcium, calcium carbonate, sodium hydrogen carbonate, sodium alginate and the like), lubricants (e.g., magnesium stearate, talc, hydrogenated vegetable oil, macrogol, silicon oil and the like), surfactants (e.g., fatty acid esters and the like), plasticizers (e.g., glycerin and the
like), stabilizers (e.g., β-cyclodextrin and the like), fillers (e.g., silicon dioxides and the like), dispersants, suspenders, emulsifiers, diluents, buffers, antioxidants, bacteria inhibitors, preservatives, flavors, and the like.

The content of oxidized glutathione in the drug of the present invention is, but not particularly limited, generally 0.001-60 % by weight, preferably 0.25-50 % by weight of drug.

When the drug of the present invention is administered to a human, the dose varies depending upon the administration mode, the subject's age and body weight, etc. Usually, the drug is administered once to several times per day in an amount to give a daily dose of 0.01 g to 10 g, preferably 0.05 g to 2 g per adult in terms of oxidized glutathione. The period for administration is, but not particularly limited to, usually one day to one year, preferably one week to three months.

The drug of the present invention can be used not only for humans but also for nonhuman animals. Nonhuman animals include nohuman mammals, birds, reptiles, amphibians, fish and the like.

The preparation of the quasi-drug of the present invention is not particularly limited and may be a dosage form similar to the above-mentioned drug, as well as mouth freshener, underarm deodorant, bath dusting powder, hair growth stimulants, hair removal products, hair dyes, agents for permanent wave, bath agent, medicinal cosmetics, medicated toothpastes, and the like.

The quasi-drug of the present invention can be prepared by the method similar to the drug of the present invention.

The content of oxidized glutathione in the quasi-drug of the present invention is, but not particularly limited to, generally 0.0001-60 % by weight, preferably 0.001-50 % by weight of quasi-drug.

The use of the drug and quasi-drug of the present invention is not particularly limited as long as it is based
on an antioxidant activity and, for example, they can be used for the prophylaxis, improvement and/or treatment of various diseases primarily caused by oxidation of substances in the body, such as renal disease, cerebro-vascular disease, circulatory organ disease, cerebral infarction, high blood pressure, arteriosclerosis, aging dementia-related disease, heart disease (e.g., myocardial infarction and the like), cancer, diabetes, burn, ophthalmopathy (due to oxidative damage of the retina), stress ulcer, stomatitis, liver function disease, skin aging, stain, wrinkle, melanogenesis, and the like.

The food or beverage of the present invention includes juices; soft drinks; alcoholic beverage; teas; lactic acid bacteria beverages; milk product such as fermented milk, butter, cheese, yogurt, processed milk and defatted milk; animal meat products such as ham, sausage and hamburger; fish cake products such as plate-like fish cake or kamaboko in Japanese, pipe-like fish cake or chikuwa in Japanese, and fried fish cake or satsumaage in Japanese; egg products such as rolled egg with soup or dashimaki in Japanese and egg-tofu; confectioneries such as cookie, jelly, chewing gum, candy, drop and snack; frozen dessert such as ice cream, sherbert and iced lolly; breads; noodles; pickles; smoked food products; dried fishes; fishes boiled in soy sauce or tsukudani in Japanese; salt curing products; soups; condiments; food materials; food additives; or any other forms. The form of the food and beverage is not particularly limited, and may be in any form, such as solid, powdery, liquid, gel, and slurry forms, so far as it is in a form that is easily ingested. The food or beverage includes the feed for nonhuman animals.

Further the food or beverage of the present invention may be in the forms of powdery foods; sheet-like foods; bottled foods; bottled beverages; retort foods; capsule foods; tablet-like foods; fluid foods; nutritious supplement drinks or the like.
An additive generally employed in foods and beverages as needed, for example, additives listed in Food Additives Indication Pocket Book (Japan Food Additives Association, January 6, 1997) such as sweeteners, coloring agents, preservatives, thickening stabilizers, antioxidants, color developing agents, bleaching agents, fungicides, gum bases, bitter agents, enzymes or enzyme sources, gloss agents, sour agents, seasonings, emulsifiers, fortifier dietary supplements, additional materials for preparation, flavors, spice extracts and the like may be added to the food or beverage of the present invention as needed, in addition to oxidized glutathione.

Examples of the sweetener include aspartame, licorice, stevia, xylose and Momordica grosvenori, sugar, starch syrup, corn syrup, and the like.

Examples of the coloring agent include carotenoid, turmeric pigment, flavonoid, caramel pigment, oriental gromurell pigment, spirulina pigment, chlorophyll, red sweet potato pigment, red Chinese yam pigment, perilla pigment, blueberry pigment, and the like.

Examples of the preservative include sodium sulfite, benzoic acid and benzoates, extract of Aralia cordata, Japanese Styrax benzoin extract, Rumpet roman extract, sorbic acid and sorbates, propionic acid and propionates, and the like.

Examples of the thickening stabilizer include gums such as gum arabic and xanthane gum, alginic acid and alginates, chitin, chitosan, aloe arborescens extract, guar gum, hydroxypropyl cellulose, casein sodium, corn starch, carboxymethylcelluloses, gelatin, agar, dextrin, methyl cellulose, polyvinyl alcohol, microfibrous cellulose, microcrystalline cellulose, seaweed cellulose, sodium polyacrylate, sodium polyphosphate, carrageenan, yeast cell wall, extract of konjac, nata de coco, mannan and the like.

Examples of the antioxidant include vitamin C, sodium
ethylenediaminetetraacetate, calcium ethylenediaminetetraacetate, erythorbic acid, oryzanol, catechin, quercetin, clove extract, enzyme-treated rutin, apple extract, sesame oil extract, dibutylhydroxytoluene, fennel extract, horseradish extract, water dropwort extract, tea extract, Tempeh extract, extract of Houttuynia cordata, tocotrienol, tocopherols, rapeseed oil extract, green coffee extract, sunflower seed, ferulic acid, butylhydroxyanisole, blueberry leaf extract, propolis extract, hego-ginkgo leave extract, hesperetin, pepper extract, garden balsam extract, gallic acid, myrica extract, eucalyptus extract, rosemary extract and the like.

Examples of the color developing agent include sodium nitrite and the like.

Examples of the bleaching agents include sodium sulfite and the like.

Examples of the fungicide include orthophenylphenol and the like.

Examples of the gum base include methyl acetylorcinoleate, Japanese lacquer wax, ester gum, elemi resin, urucury wax, ozokerite, opopanax resin, kauri gum, carnauba wax, guaiacum resin, gutta katiau, gutta hangkang, gutta percha, glycerin fatty acid ester, spermaceti wax, copaiba balsam, copal resin, gum, rice bran wax, sugar cane wax, shellac, jelutong, sucrose fatty acid ester, sorba, sorbitan fatty acid ester, talc, calcium carbonate, dammar resin, chicle, chilte, tunu, low molecular weight gum, paraffin wax, fir balsam, propylene glycol fatty acid ester, powdered pulp, powdered rice husks, jojoba wax, polyisobutylene, polybutene, microcrystalline wax, mastic, massanduruba chocolate, beeswax, calcium phosphate and the like.

Examples of the bitter agent include isoalpha bitter acid, caffeine, kawaratake extract, cinchona extract, Amur cork extract, gentian extract, spice extracts, enzyme-treated
naringin, Jamaica quassia extract, theobromine, naringin, bitter ash extract, warmwood extract, isodonis extract, himematsutake extract, borapet, methyl thioadenosine, litchi extract, olive tea, sour orange extract, hop extract, mugwort extract and the like.

Examples of the enzyme or enzyme source include amylase, trypsin, rennet, lactic acid bacteria and the like.

Examples of the gloss agent include Japanese lacquer wax, Japan wax and the like.

Examples of the sour agent include adipic acid, itaconic acid, citric acid and citrates, succinic acid and succinates, sodium acetate, tartaric acid and tartrates, carbon dioxide, lactic acid, phytic acid, fumaric acid, malic acid, phosphoric acid and the like.

Examples of the seasoning include amino acids such as asparagine, aspartic acids, glutamic acid, glutamine, alanine, isoleucine, glycine, serine, cystine, tyrosine, leucine and proline, nucleic acids such as sodium inosinate, sodium uridylate, sodium guanylate, sodium cytidylate, calcium ribonucleotide and sodium ribonucleotide, organic acids such as citric acid and succinic acid, potassium chloride, sodium chloride-decreased brine prepared from salt lake water, crude potassium chloride from sea water, whey salt, tripotassium phosphate, dipotassium hydrogenphosphate, potassium dihydrogenphosphate, disodium hydrogenphosphate, sodium dihydrogenphosphate, trisodium phosphate, chlorella extract and the like.

Examples of the fortifier dietary supplement include zinc salts, vitamin C, various amino acids, 5-adenylic acid, iron chloride, hesperidin, various kinds of burnt calcium, various kinds of unburnt calcium, dibenzoylthiamine, calcium hydroxide, calcium carbonate, thiamine hydrochloride, dunaliella carotene, tocopherol, nicotinic acid, carrot carotene, palm oil carotene, calcium pantothenate, vitamin A, hydroxyproline, calcium dihydrogenpyrophosphate, ferrous
pyrophosphate, ferric pyrophosphate, ferritin, heme iron, menaquinone, folic acid, riboflavin and the like.

Examples of the additional material for preparation include processing aids such as acetone and ion exchange resin, extract of fig leaf, extract of rice straw ash, kaolin, glycerin fatty acid ester, mulberry extract, bone ash, extract of perilla, extract of ginger, various tannins, phaffia color, extract of grape seed, ethanol and the like.

The content of oxidized glutathione in the food or beverage of the present invention is, but not particularly limited to, generally 0.0001-100 % by weight, preferably 0.001-99 % by weight of food or beverage.

The food or beverage of the present invention can be used as those for the prophylaxis and/or improvement of various diseases primarily caused by oxidation of substances in the body, such as renal disease, cerebro-vascular disease, circulatory organ disease, cerebral infarction, high blood pressure, arteriosclerosis, aging dementia-related disease, heart disease (e.g., myocardial infarction and the like), cancer, diabetes, burn, ophthalmopathy (due to oxidative damage of the retina), stress ulcer, stomatitis, liver function disease, skin aging, stain, wrinkle, melanogenesis, and the like; for example, health food, health-conscious food, functional food, nutritionaid food, food for specified health uses, patient food, food for those having difficulty in swallowing, medical food and the like.

The form of the cosmetic composition of the present invention includes, but not particularly limited to, basic cosmetics such as general creams, emulsions (e.g., cleansing cream, cold cream, vanishing cream, hand cream and the like), shaving cream (e.g., after shave cream, shaving cream and the like), skin lotion (e.g., hand lotion, general cosmetic lotion and the like), cologne, shaving lotion (e.g., after shaving lotion, shaving lotion and the like), cosmetic oils, and packs; makeup cosmetics such as skin whiteners (e.g.,
whitening cream, whitening solids, whitening powder, talcum powder, whitening paste, body powder, whitening water and the like), powder, foundation (as cream, liquid, solid or the like), rouge, eyebrow pencil, eye cream, eye shadow and mascara; cleaning cosmetics such as cosmetic soaps, facial washes (as cream, paste, liquid, gel, granule, outer, aerosol or the like), shampoo, and rinse; whitening cosmetics; anti-aging cosmetics; scalp and hair cosmetics such as hair dyes, hair treatments (as cream, mist, oil, gel or the like), split end coating agents and hair setting agents (e.g., hair grease, setting lotion, curling lotion, pomade, stick, fragrant hair oil, hairspray, hair mist, hair liquid, hair foam, hair gel, water grease and the like); perfumes such as standard perfume, paste perfume and powder perfume; suntan and sunblock cosmetics such as suntan or sunblock creams, suntan or sunblock lotions and suntan or sunblock oils; eyeliner cosmetics; mouth and lip cosmetics such as lipstick and lip creams; oral cosmetics such as toothpaste; and bath cosmetics such as bath salt, bath oil and bubble bath.

The cosmetic composition of the present invention may contain, besides oxidized glutathione, appropriate amounts of other known components according to the desired form, and can be prepared by ordinary method. Examples of other components include water (such as purified water, deep-water), ester-type oil, hydrocarbon-type oil, silicone-type oil, fluorine-containing oil, animal and plant oils, water-soluble polymer, fat-soluble polymer, emollient, nonionic surfactant, anionic surfactant, cationic surfactant, ampholytic surfactant, gelling agent, organic or inorganic pigment, organic powder, antiseptic, plant extract, pH adjustor, alcohol, pigment, perfume and the like. Furthermore, cooling agent and deodorant may be contained by its purpose.

Examples of the ester-type oil include esters such as glyceryl tri-2-ethylhexanoate, cetyl 2-ethylhexanoate, isopropyl myristate, butyl myristate, isopropyl palmitate,
ethyl stearate, octyl palmitate, isocetyl isostearate, butyl stearate, ethyl linoleate, isopropyl linoleate, ethyl oleate, isocetyl myristate, isostearyl myristate, isostearyl palmitate, octyldodecyl myristate, isocetyl isostearate, diethyl sebacate, diisopropyl adipate, glyceryl tri (capryl-caprate), trimethylolpropane tri-2-ethylhexanoate, trimethylolpropane triisostearate, pentaerythritol tetra-2-ethylhexanoate, cetyl caprylate, decyl laurate, hexyl laurate, decyl myristate, myristyl myristate, cetyl myristate, stearyl stearate, decyl oleate, cetyl ricinoleate, isostearyl laurate, isotridecyl myristate, isocetyl palmitate, octyl stearate, isocetyl stearate, isodecyl oleate, octyldodecyl oleate, octyldodecyl linoleate, isopropyl isostearate, cetostearyl 2-ethylhexanoate (mixture of cetyl 2-ethylhexanoate and stearyl 2-ethylhexanoate), stearyl 2-ethylhexanoate, hexyl isostearate, ethylene glycol dioctanoate, ethylene glycol dioleate, propylene glycol dicaprate, propylene glycol di- (capryl-caprate), propylene glycol dicaprylate, neopentylglycol dicaprate, neopentylglycol dioctanoate, glyceryl tricaprylate, glyceryl triundecylate, glyceryl triisopalmitate, glyceryl triisostearate, octyldodecyl neopentanoate, isostearyl octanoate, octyl isononanoate, hexyldecyl neodecanoate, octyldodecyl neodecanoate, isocetyl isostearate, isostearyl isostearate, octyldecyl isostearate, polyglycerol olate, polyglycerol isostearate, triisocetyl citrate, triisooctyl citrate, lauryl lactate, myristyl lactate, cetyl lactate, octyldecyl lactate, triethyl citrate, acetyltriethyl citrate, acetyltributyl citrate, trioctyl citrate, diisostearyl maleate, 2-ethylhexyl hydroxystearate, di- (2-ethylhexyl) sulfosuccinate, diisobutyl adipate, diisopropyl sebacate, dioctyl sebacate, cholesteryl stearate, cholesteryl isostearate, cholesteryl hydroxystearate, cholesteryl olate, dihydrocholesteryl olate, phytosteryl isostearate, phytosteryl olate, isocetyl 12-stearoylhydroxystearate, stearyl 12-stearoylhydroxystearate and isostearyl 12-stearoylhydroxystearate.
Examples of the hydrocarbon-type oil include squalane, liquid paraffin, alpha-olefin oligomer, isoparaffin, ceresine, paraffin, liquid isoparaffin, polybutene, microcrystallinewax, Vaseline and the like.

Examples of the silicone-type oil include polymethyl silicone, methylphenylsilicone, methylcyclopolsiloxane, octamethylpolysiloxane, decamethylpolysiloxane, dodecamethylcyclosiloxane, dimethyl siloxane-methylcetyloxysiloxane copolymer, dimethylsiloxane-methylstearoyloxy siloxane copolymer, alkyl-modified silicone oil, amino-modified silicone oil and the like.

Examples of the fluorine-containning oil include perfluoropolyether and the like.

Examples of the animal and plant oils include avocado oil, almond oil, olive oil, sesame oil, rice bran oil, safflower oil, soybean oil, corn oil, rapeseed oil, apricot oil, palm kernel oil, palm oil, castor oil, sunflower oil, grape seed oil, cotton seed oil, coconut oil, kukui nut oil, wheat embryo oil, rice embryo oil, shea butter, evening primrose oil, macadamia nut oil, meadow foam oil, yolk oil, tallow, horse oil, mink oil, orange roughy oil, jojoba oil, lanolin, pristane and the like.

Examples of the water-soluble polymer include carboxyvinyl polymer, polyaspartic acid salt, tragacanth, xanthane gum, methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, carboxymethylcellulose, water-soluble chitin, chitosan, dextrin and the like.

Examples of the fat-soluble polymer include polyvinylpyrrolidone-eicosene copolymer, polyvinylpyrrolidone-hexadecene copolymer, nitrocellulose, dextrin fatty acid ester, polymeric silicone and the like.

Examples of the emollient include cholesteryl long-chain-acylglutamate, cholesteryl hydroxystearate, 12-
hydroxystearic acid, stearic acid, rosic acid, lanolin fatty acid cholesteryl ester and the like.

Examples of the nonionic surfactant include propylene glycol fatty acid ester, glycerol fatty acid ester, polyglycerol fatty acid ester, sorbitan fatty acid ester, POE (polyoxyethylene) sorbitan fatty acid ester, POE sorbitol fatty acid ester, POE glycerol fatty acid ester, POE alkyl ether, POE fatty acid ester, POE hardened castor oil, POE castor oil, POE/POP (polyoxypropylene) copolymer, POE/POP alkyl ether, polyether-modified silicone, alkanolamide laurate, alkylamine oxide, hydrogenated soybean phospholipid and the like.

Examples of the anionic surfactant include fatty acid soap, alpha-acyl sulfonate, alkyl sulfonate, alkylallyl sulfonate, alkynaphthalene sulfonate, alkyl sulfate, POE alkyl ether sulfate, alkylamide sulfate, alkyl phosphate, POE alkyl phosphate, alkylamide phosphate, alkylolylalkyl taurate, N-acyl amino acid salt, POE alkyl ether carboxylate, alkyl sulfosuccinate, sodium alkylsulfocacetate, acylated collagen hydrolyzate peptide salt, perfluoroalkyl phosphate and the like.

Examples of the cationic surfactant include alkyltrimethylammonium chloride, stearyltrimethylammonium chloride, stearyltrimethylammonium bromide, cetostearyltrimethylammonium chloride (mixture of stearyltrimethylammonium chloride and cetyltrimethylammonium chloride), distearyldimethylammonium chloride, stearyldimethylbenzylammonium chloride, behenyltrimethylammonium bromide, benzalkonium chloride, diethylaminoethylamide stearate, dimethylaminopropylamide stearate, lanolin derivative quaternary ammonium salt and the like.

Examples of the ampholytic surfactant include ampholytic surfactants such as carboxybetaine-type, amidobetaine-type, sulfobetaine-type, hydroxysulfobetaine-type,
amidosulfobetaine-type, phosphobetaine-type, aminocarboxylic acid salt-type, imidazoline derivative-type and amidoamine-type.

Examples of the gelling agents include amino acid derivatives such as N-lauroyl-L-glutamic acid and 1,3-diaminobutane; dextrin fatty acid esters such as dextrin palmitate, dextrin stearate, and dextrin 2-ethylhexane palmitate; sucrose fatty acid esters such as sucrose palmitate and sucrose stearate; benzylidene derivatives of sorbitol such as monobenzylidene sorbitol and dibenzylidene sorbitol; clay minerals modified with an organic moiety such as dimethylbenzyldodecylammonium montmorillonite clay and dimethyldioctadecylammonium montmorillonite; and the like.

Examples of the inorganic or organic pigment include inorganic pigments such as silicic acid, silicic anhydride, magnesium silicate, talc, sericite, mica, kaolin, red oxide, clay, bentonite, titanium-coated mica, bismuth oxychloride, zirconium oxide, magnesium oxide, zinc oxide, titanium oxide, aluminum oxide, calcium sulfate, barium sulfate, magnesium sulfate, calcium carbonate, magnesium carbonate, iron oxide, ultramarine, chromium oxide, chromium hydroxide, calamine and carbon black; organic pigments such as polyamide, polyester, polypropylene, polystyrene, polyurethane, vinyl resin, urea resin, phenolic resin, fluoro resin, silicon resin, acrylic resin, melamine resin, epoxy resin, polycarbonate resin, divinylbenzene-styrene copolymer, silk powder, cellulose, CI pigment yellow, CI pigment orange and the like; and composite powder of these inorganic pigments and organic pigments, and the like.

Examples of the organic powder include metallic soaps such as calcium stearate; alkylphosphate polyvalent metallic salts such as zinc sodiumcetylphosphate, zinc laurylphosphate and calcium laurylphosphate; acylamino acid polyvalent metal salts such as N-lauroyl-beta-alanine calcium salt, N-lauroyl-beta-alanine zinc-salt and N-lauroylglycine calcium salt;
amidosulfonic acid polyvalent metal salts such as N-
lauroyltauline calcium salt and N-palmitoyltaurine calcium
salt; N-acyl basic amino acid such as N epsilon-lauroyllysine,
N epsilon-palmitoyllysine, N alpha-palmitoylornitine, N alpha-
lauroylarginine and N alpha-hardened tallow fatty acid
acylarginine; N-acyl polypeptides such as N-
lauroylglycylglycine; alpha-amino fatty acids such as alpha-
aminocaprylic acid and alpha-aminolauric acid; polyethylene,
polypropylene, nylon, polymethyl methacrylate, polystyrene,
divinylbenzene-styrene copolymer, ethylene tetrafluoride and
the like.

Examples of the antiseptic include methyl paraben,
propyl paraben and the like.

Examples of the plant extract include extract of
angelica keiskei, extract of avocado, extract of hydrangea
leaves, extract of althaea, extract of arnica, extract of aloe,
extact of apricot, extract of apricot kernel, extract of
ginkgo, extract of fennel, extract of turmeric, extract of
oolong tea, extract of rose fruits, extract of echinacea leaf,
extact of Scutellaria root, extract of phellodendron bark,
extact of Japanese coptis, extract of wheat, extract of
hypericum, extract of lamium, extract of nasturtium, extract
of orange, extract of chamomile, extract of carrot, extract of
artemisia, extract of licorice, extract of carcade, extract of
pyracantha fortuneana, extract of kiwi, extract of cinchona,
extact of cucumber, extract of gardenia, extract of sasa
albo-marginata, extract of sophora, extract of walnut, extract
of grapefruit, extract of clematis, extract of chlorella,
extact of mulberry, extract of gentian, extract of black tea,
extact of comfrey, collagen, extract of cowberry, extract of
asiasarum root, extract of bupleurum root, extract of
melilotus, extract of salvia, extract of soapwort, extract of
bamboo grass, extract of hawthorn, extract of Japanese pepper,
extact of shiitake, extract of rehmannia glutinosa, extract
of lithospermum root, extract of labiate, extract of Japanese
linden, extract of Filipendula multijuga, extract of Paeonia lactiflora, extract of Japanese iris root, extract of white birch, extract of field horsetail, extract of English ivy, extract of Crataegus monogyna, extract of Sambucus nigra, extract of Achillea millefolium, extract of lemon balm, extract of sage, extract of common mallow, extract of Cnidium rhizome, extract of Swertia japonica, extract of soybean, extract of jujube, extract of thyme, extract of tea plant, extract of clove, extract of cogan, extract of citrus unshiu peel, extract of Japanese angelica root, extract of calendula, extract of peach kernel, extract of bitter orange peel, extract of houttuynia cordata, extract of tomato, extract of ginseng, extract of garlic, extract of wild rose, extract of hibiscus, extract of ophiopogon tuber, extract of parsley, beeswax, extract of hamamelis, extract of pellitory, extract of plectranthus japonicus, bisabolol, extract of loquat, extract of tussilago farfara, extract of butterbur flower, extract of pachyma hoelen, extract of butcher's bloom, extract of grape, propolis, extract of sponge cucumber, extract of safflower, extract of pepper mint, extract of linden, extract of Paeonia suffruticosa, extract of hop, extract of pine, extract of horse chestnut, extract of lysichiton, extract of soapberry, extract of melissa, extract of peach, extract of comflower, extract of eucalyptus, extract of saxifrages, extract of citron, extract of coix seed, extract of mugwort, extract of lavender, extract of apple, extract of lettuce, extract of lemon, extract of Chinese milk vetch, extract of rose, extract of rosemary, extract of Roman chamomile and the like.

Examples of the pH adjustor include citric acid, sodium citrate, malic acid, sodium malate, fumaric acid, sodium fumarate, succinic acid, sodium succinate, sodium hydroxide, disodium hydrogenphosphate, sodium pyrrolidonecarboxylate and the like.

Examples of the alcohol include lower alcohol such as
methanol, ethanol, isopropyl alcohol, n-propyl alcohol, t-butyl alcohol and s-butyl alcohol; liner fatty alcohol such as lauryl alcohol, cetyl alcohol, stearyl alcohol, behenyl alcohol, myristyl alcohol, oleyl alcohol and cetostearyl alcohol; branched fatty alcohol such as monostearylglycerin ether (butyl alcohol), 2-decyltetradecinol, lanolin alcohol, cholesterol, phytosterol, hexyldodecanol, isostearyl alcohol and octyldodecanol, and the like.

The pigment and perfume are not particularly limited as long as it is generally used for cosmetic compositions or skin external preparations.

Examples of the cooling agent include 1-menthol or derivative thereof, N-substituted-p-menthane-3-carboxamides, 3-substituted-p-menthane, 2- or 3-substituted-p-menthane diol, trialkyl-substituted cyclohexanecarboxamide, isopulegol and the like.

Examples of the deodorant include astringent single salts such as aluminum chloride, aluminum oxychloride, basic aluminum bromide, aluminum sulfate, aluminum chlorohydrate, aluminum zirconium chlorohydrate, zinc sulfate, phenolsulfonate and basic aluminum zinc lactate; and complexes of these single salts with glycol or amino acid.

The content of oxidized glutathione in the cosmetic composition of the present invention is, but not particularly limited to, generally 0.0001-10 % by weight, preferably 0.001-5 % by weight of cosmetic composition.

The cosmetic composition of the present invention can also be used for the prophylaxis and/or improvement of unpreferable changes and aging of the skin (e.g., blemishes, freckles, wrinkles, decreased elasticity, dye deposition, melanin dye formation etc.) primarily caused by increase of active oxygen concentration, thereby-caused lipoperoxide formation and the like, and the like.

Examples

The present invention is explained in more detail in the
following by referring to Examples, which are not to be constructed as limitative. In the following description, "parts" and "%" mean "parts by weight" and "% by weight" respectively, unless otherwise specified.

EXAMPLE 1

[Preparation of Face Lotion Containing Oxidazed Glutathione]

A lotion having the following composition is prepared.

(1) Oxidazed Glutathione 0.1 g
(2) Propylene glycol 3.0 g
(3) Sodium pyrrolidonecarboxylate 0.3 g
(4) Methylparaben 0.1 g
(5) Polyoxyethylene polyoxypropylene alkyl ether 1.0 g
(6) Ethanol 10.0 g
(7) Fragrance suitable quantity
(8) Purified water suitable quantity

The aqueous layer ingredients (1) to (4) and (8) are mixed and dissolved under heating at 60°C. Then, the oily layer ingredients (5) to (7) mixed and dissolved are added to the solution. The mixture is stirred to give a homogeneous mixture. Then the mixture is cooled and filtered to give a lotion.

EXAMPLE 2

[Preparation of Emulsion Containing Oxidazed Glutathione]

Oil phase components: Squalane 4.0 g, Wheat germ oil 2.0 g, Monoglyceryl stearate 1.0 g, Polyoxyethylene stearyl ether 4.0 g, Propylparaben 0.1 g

Aqueous phase components: glycine 0.5 g, oxidazed glutathione 0.1 g, Methylparaben 0.2 g, Propylene glycol 0.1 g, Polyethylene glycol 6000 0.2 g, Sodium hyaluronate 0.05 g, Purified water 86.75 g

Each of the oil phase components and the aqueous phase components are homogenized by heating at 80°C, and then the aqueous phase is added to the oil phase under stirring to give an emulsion.
EXAMPLE 3

[Preparation of Cream Containing Oxidazed Glutathione]

A cream having the following composition is prepared.

(1) Beeswax 4.0 g
(2) Cetanol 5.0 g
(3) Stearic acid 5.0 g
(4) Lanoline 3.0 g
(5) Pristane 25.0 g
(6) Polyoxyethylene stearyl ether 3.5 g
(7) Glyceryl monostearate 1.5 g
(8) Oxidazed Glutathione 2.0 g
(9) Propylene glycol 10.0 g
(10) Purified water suitable quantity
(11) Fragrance, preservative suitable quantity

The oily layer ingredients (1) to (7) and the aqueous layer ingredients (8) to (11) are dissolved under heating at 80°C, respectively. Then, the oily layer mixture is gradually added to the aqueous layer mixture while they are emulsified in a homomixer. The mixture is stirred to give a homogeneous mixture. And the mixture is cooled to give a cream.

EXAMPLE 4

[Production of a Tablet Containing Oxidazed Glutathione]

60.0 kg of Oxidazed Glutathione; 36.0 kg of a fine cellulose crystal; 6.6 kg of sucrose fatty acid ester; 1.2 kg of calcium phosphate; and 20.0 kg of beta-cyclodextrin are mixed. The mixture obtained is compressed and molded to a tablet of 250 mg with 8 mm of diameter.

EXAMPLE 5

[Production of an Enteric Capsule Containing Oxidazed Glutathione]

20 kg of the mixture produced in Example 4 and 0.2 kg of silicon dioxide are mixed and stirred. The mixture obtained is put into a capsule-filling machine to fill 20,000 tablets of gelatin Number 2 hard-capsules to provide the hard-capsules.
The surfaces of the hard-capsules obtained are coated with a zein solution to produce 20,000 enteric capsules containing oxidazed glutathione.

EXAMPLE 6

Chewing gum is prepared by the ordinary method with the recipe; oxidazed glutathione 1.5 g, gum base 25 g, sugar 63 g, millet syrup 10 g, and flavoning 1 g.

EXAMPLE 7

The drop is prepared using the candy base material (Maltitol 35 kg, Corn syrup 43° Baume 21 kg) and Antioxidant mixture (Polyethylene glycol 2.75 kg, Oxidazed glutathione 35 kg, Citric acid 60 kg, Wild cherry artificial flavor 60 g).

The preparation of the candy base material is conducted as follows.

The maltitol is dissolved in 5.5 liters of water. Glucose-containing corn syrup is added to and mixed with the solution-obtained. At this point, colorings are added as needed to obtain the desired color. For the coloring, those that can adequately dissolve are used.

The above mixture is placed in a steam jacket kettle heated to 125°C. From there, the mixture is placed in a storage container by a pump, and this is supplied to a continuous cooker. By passing the coil of the cooker, the syrup reaches a temperature of 125-150°C. Afterwards, this is supplied by a steam vacuum ejector to a receiving kettle maintained at a vacuum of 28-29 inches for approximately 6-7 minutes. During this time, water is removed until the water content is reduced to approximately 1% or less, and a suitable melted candy base material is formed. By slowly cooling the melted candy base material, the candy base material is prepared.

Next, the oxidazed glutathione, citric acid, and artificial flavor (powder) is added to polyethylene glycol to
prepare the antioxidant mixture. This mixture is heated to approximately 90°C to make into a fluid. The resulting heated fluid antioxidant mixture is rapidly added to the melted candy base material (in which the temperature has been lowered to approximately 100°C or to a temperature slightly below that).

Next, after adequately kneading the entire mass, this is transferred to a spinning machine. By extruding into a lozenge shaped die, drops containing oxidazed glutathione are prepared.

EXAMPLE 8
[Preparation of Drops Containing Oxidazed Glutathione (2)]

The melted candy mass added with the antioxidant mixture obtained in Example 7 is poured onto a cooling table. After solidifying to a semi-solid mass on the cooling table, this is molded into the desired shape for the intake of unit intake amounts of oxidazed glutathione. With this, drops containing oxidazed glutathione are prepared.

EXAMPLE 9
[Production of Drink Containing Oxidazed Glutathione]

0.6 kg of oxidazed glutathione, 3 kg of erythritol, 0.05 Kg of citric acid, 3 g of an artificial sweetener, and 0.06 kg of a flavor are stirred and dissolved in 50 L of water at a solution temperature of 70°C. After the pH of the solution is adjusted to 3.3, the solution is sterilized using plate sterilization and filled into a bottle. The bottle is sterilized using a pasteurizer to produce a drink.

Industrial Applicability

According to the present invention, an antioxidant composition available for various use can be provided, since oxidized glutathione has antioxidative activity same as glutathione, has high stability, and does not develop unpleasant odor.

This application is based on a patent application No. 2010-253075 filed in Japan, the contents of which are hereby incorporated by reference.
1. An antioxidant composition comprising oxidized glutathione.

2. The composition of claim 1, wherein the composition is a cosmetic composition.

3. The composition of claim 1, wherein the composition is a food or beverage.
**INTERNATIONAL SEARCH REPORT**

**International application No.**

PCT/JP2011/076595

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### A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl. A61K8/64 (2006.01) i, A63L1/305 (2006.01) i, A61K38/00 (2006.01) i, A61P17/18 (2006.01) i, A61P39/06 (2006.01) i, A61Q19/08 (2006.01) i

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### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl. A61K8/64, A61L1/305, A61K38/00, A61P17/18, A61P39/06, A61Q19/08

Documented searched other than minimum documentation to the extent that such documents are included in the fields searched

- Published examined utility model applications of Japan 1922-1996
- Published unexamined utility model applications of Japan 1971-2012
- Registered utility model specifications of Japan 1996-2012
- Published registered utility model applications of Japan 1994-2012

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

CA/ REGISTRY (ETN), JSTPlus/ JMEDPlus / IST7 58 Κ (JDreaml)

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### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>WO 2009/001884 A1 (KYOWA HAKKO BIO CO., LTD.) 2008.12.31, claims 1-5, [0005], examples 1-3</td>
<td>1-3</td>
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<tr>
<td>X</td>
<td>JP 9-067227 A (NOEVIR KK) 1997.03.11, [0002], [0003], tables 1, 2, 3-1, 3-2</td>
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<td>JP 5-301811 A (KYOWA HAKKO KOGYO KK) 1993.11.16, claim 1, tables 1-3, examples 3, 7 &amp; US 5316767 A</td>
<td>1, 2</td>
</tr>
</tbody>
</table>

**☑** Further documents are listed in the continuation of Box C. 

**See patent family annex.**

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### DOCUMENTS CONSIDERED TO BE RELEVANT

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