ORAL CARE COMPOSITION COMPRISING ISOBUTYL MAGNOLOL

BACKGROUND

[0001] There is a need for safe, effective antibacterial and anti-inflammatory agents for use in oral care compositions. Magnolia extract is known to contain compounds having antibacterial and/or anti-inflammatory properties, and such compounds have been the focus of considerable interest for use in oral care compositions. The use of such compounds in oral care compositions is described, for example, in WO2001/085116, WO 2011/106492 and WO 2011/106493, the contents of which application are incorporated herein by reference. Synthetic non-natural analogs of various components of magnolia extract are also known to have antibacterial activity. Isobutyl magnolol (5,5'-di(2-methylpropyl)-biphenyl-2,2'-diol) is a promising anti-bacterial and anti-inflammatory active for oral care use. Synthesis of this compound, but not its use for oral care indications, is described in WO2010/042313. However, the extremely poor solubility of isobutyl magnolol both in water and in oil, and its strong tendency to crystallize out from the composition matrix in a variety of surfactant systems significantly limit its antibacterial potential and disfavor its use in an oral care formulation. There is a need for oral care compositions that are both orally acceptable and capable of solubilizing isobutyl magnolol.

SUMMARY

[0002] It is now surprisingly discovered that adding propylene glycol monolaurate to a composition comprising isobutyl magnolol greatly enhances its solubility in the composition and significantly improves the inhibition zone in a zone inhibition test. Addition of propylene glycol monolaurate significantly improves the antibacterial efficacy of toothpaste formulas containing isobutyl magnolol.

[0003] In one embodiment, therefore, the invention provides oral care compositions, for example toothpastes, comprising isobutyl magnolol and propylene glycol monolaurate, as well as methods of making and using such compositions.

[0004] Further areas of applicability of the present invention will become apparent from the detailed description provided hereinafter. It should be understood that the detailed description and specific examples, while indicating the preferred embodiment of the invention, are intended for purposes of illustration only and are not intended to limit the scope of the invention.

DETAILED DESCRIPTION

[0005] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the invention, its application, or uses.

[0006] In a first embodiment, the invention provides an oral care composition (Composition 1), for example a toothpaste, comprising isobutyl magnolol and propylene glycol monolaurate. For example, the invention provides oral care compositions as follows:

1.1. Composition 1 in the form of a toothpaste;

1.2. Composition 1 in the form of a mouthrinse;

1.3. Any of the foregoing compositions wherein the isobutyl magnolol is present in an antibacterially effective concentration;

1.4. Any of the foregoing compositions comprising an antibacterially effective amount of isobutyl magnolol and an amount of propylene glycol monolaurate effective to solubilize the isobutyl magnolol in an orally acceptable carrier;

1.5. Any of the foregoing compositions wherein the concentration of isobutyl magnolol is from 0.1-3%, e.g., about 1-2%, based on the total weight of the composition;

1.6. Any of the foregoing compositions wherein the ratio by weight of isobutyl magnolol to propylene glycol monolaurate is from 0.2:1 to 2:1, e.g., about 1:1;

1.7. Any of the foregoing compositions further comprising polyethylene glycol, e.g., PEG 600, e.g., in an amount of 0.5-5% by weight, e.g., in a ratio of about 2:1 relative to the isobutyl magnolol;

1.8. Any of the foregoing compositions further comprising a humectant, e.g., glycerin, sorbitol, or mixtures thereof, e.g., in an amount by weight of about 30%-70%, e.g., 40-60%, e.g., about 50%;

1.9. Any of the foregoing compositions further comprising an anionic surfactant, e.g., sodium lauryl sulfate, e.g., in an amount of 0.5-5%, e.g., about 2%;

1.10. Any of the foregoing compositions further comprising an effective amount of a fluoride ion source, e.g., sodium fluoride, e.g., in an amount by weight of 0.1-0.5%, e.g., about 0.34%;

1.11. Any of the foregoing compositions further comprising flavoring, e.g., selected from non-caloric sweeteners, e.g., saccharine, herbal flavorings (e.g., mint flavor), and combinations thereof;

1.12. Any of the foregoing compositions further comprising an abrasive material, e.g., silica abrasive, precipitated calcium carbonate, or combinations thereof;

1.13. Any of the foregoing compositions comprising the following ingredients:

Ingredient	% by weight
PEG600	1-4%, e.g., about 2.8%
Flavor	0-3%, e.g., about 1.4%
Isobutyl magnolol	0.5-3%, e.g., about 1.4%
propylene glycol monolaurate	0.5-3%, e.g., about 1.4%
Glycerin	20-30%, e.g., about 25%
Sorbitol	20-30%, e.g., about 25%
Sodium Saccharine	0.1-0.7%, e.g., about 0.4%
Sodium Fluoride	0.1-0.7%, e.g., about 0.34
SLS	1-3%, e.g., about 2.1%
Water	As required for suitable consistency
Abrasive silica	0-20%

[0007] As used herein, the term "solubilizing effective amount" refers to the amount of an ingredient effective to sufficiently solubilize the amount of isobutyl magnolol present in an orally acceptable carrier.

[0008] In a further embodiment, the invention provides a method of treatment, prophylaxis or control of a disease or condition of the oral cavity, for example a bacterial infection or inflammatory condition in the mouth, for example gingivitis, comprising applying an oral care composition in accordance with the invention, e.g., Composition 1, et seq., to the oral cavity of a patient in need thereof. In some embodiments, the disease or condition of the oral cavity includes

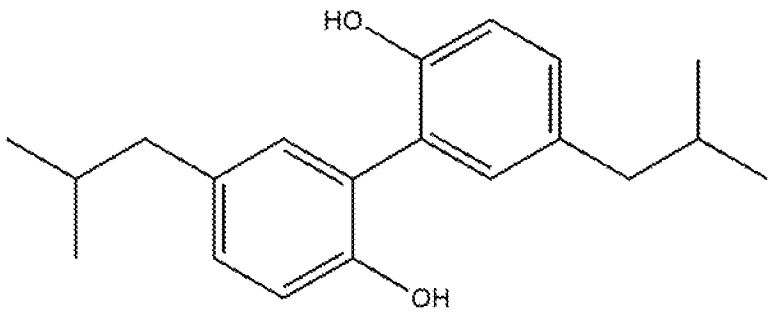
a disease or condition of the teeth, oral mucosa, gingiva or tongue. Such diseases or conditions include caries, gingivitis, periodontitis, and cosmetic conditions such as yellowing and malodour.

[0009] In a further embodiment, the invention provides the use of isobutyl magnolol and propylene glycol monolaurate in combination for the manufacture of an oral care composition, e.g., according to Composition 1 et seq., for such a method of treatment, prophylaxis or control of a disease or condition of the oral cavity.

[0010] In a further embodiment, the invention provides a method of making an oral care composition, e.g., according to Composition 1, et seq., comprising admixing propylene glycol monolaurate and isobutyl magnolol with an orally acceptable carrier.

[0011] The methods and compositions of the present embodiments impart advantages over the prior art compositions by providing an oral composition that is well solubilized, safe, and highly efficacious against bacterial infection and/or inflammation in a mammalian subject.

[0012] Magnolol (5,5'-di(prop-2-en-1-yl)-biphenyl-2,2'-diol) is a bioactive compound found in the bark of the Houpu magnolia (*Magnolia officinalis*). Isobutyl magnolol (5,5'-di(2-methylpropyl)-biphenyl-2,2'-diol) is a synthetic analog of magnolol, with antibacterial and anti-inflammatory properties, having a structure as follows:



[0013] By "orally acceptable" is meant safe for use in the mouth at levels required. In general, all components of the compositions of the present invention are orally acceptable.

[0014] The expressions "carrier" or "aqueous carrier" or "orally acceptable carrier" as used throughout this description denote any safe and effective materials for use herein. Such materials include, water, solvents, etc., that may contain a humecant such as glycerin, sorbitol, xylitol and the like. The carrier or orally acceptable carrier also may include additional dentifrice components, such as thickening agents, ionic active ingredients, buffering agents, anticalculus

agents, abrasive polishing materials, peroxide sources, alkali metal bicarbonate salts, surfactants, titanium dioxide, coloring agents, flavor systems, sweetening agents, antimicrobial agents, herbal agents, desensitizing agents, stain reducing agents, and mixtures thereof.

[0015] Orally acceptable carriers for use in the invention include the conventional and known carriers used in making toothpastes, tooth powders, prophylaxis pastes, mouth rinses, lozenges, gums, beads, and the like, and are more fully described hereinafter. It is preferred that the orally acceptable carrier does not cause irritation, swelling or pain and does not typically produce an allergic or untoward reaction such as gastric upset, nausea or dizziness. Selection of specific carrier components is dependant on the desired product form, including dentifrices, toothpastes, tooth powders, prophylaxis pastes, mouth rinses, lozenges, gums, gels, paints, confectionaries, and the like.

[0016] The term "mouthrinse" in the present invention refers to oral compositions that are substantially liquid in character, such as a mouth wash, spray, or rinse. In such a preparation the orally acceptable carrier typically has an aqueous phase comprising water or a water and alcohol mixture. Further, in various embodiments, the oral carrier includes a humectant and surfactant as described below. Generally, the weight ratio of water to alcohol is in the range of in an amount of 1: 1 to 20: 1, preferably 3: 1 to 10: 1 and more preferably 4: 1 to 6: 1. The total amount of water- alcohol mixture in this type of preparation is typically in an amount of 70 to 99.9% of the preparation. In various embodiments, the alcohol is typically ethanol or isopropanol.

[0017] As recognized by one of skill in the art, the orally acceptable carrier of the present invention may also comprise a variety of other conventional active ingredients known to one of skill in the art, including anti-plaque agents, whitening agents, antibacterial agents, tartar control (anticalculus) agent, anti-caries agents, sensitivity agents, and the like. Preferably, the carrier does not substantially reduce the efficacy of the isobutyl magnolol.

[0018] The pH of such liquid and other preparations of the oral composition of the present invention is generally in an amount of 4.5 to 10. The pH can be controlled with acid (e.g., citric acid or benzoic acid) or base (e.g., sodium hydroxide) or buffered (with sodium citrate, benzoate, carbonate, or bicarbonate, disodium hydrogen phosphate, or sodium dihydrogen phosphate, for example).

[0019] In various embodiments, the aqueous oral composition (e.g., mouthrinse) contains a humectant. The humectant is generally a mixture of humectants, such as glycerin and sorbitol,

and a polyhydric alcohol such as hexylene glycol, or polyethylene glycol, although the use of polyethylene glycol as a humectant in addition to its use to enhance the solubility of the active ingredient is optional. The humectant content for a mouth rinse typically is in the range of 5 to 40% and preferably 10 to 30%.

[0020] Surfactants suitable for compositions of the present invention include anionic, nonionic, and zwitterionic surfactants. The surfactant usually is present in the aqueous oral compositions of the present invention in an amount of 0.01% to 5%, preferably in an amount of 0.5% to 2.5%.

[0021] The oral composition according to the present invention may optionally include other materials, such as for example, cleaning agents, flavouring agents, sweetening agents, adhesion agents, surfactants, foam modulators, abrasives, pH modifying agents, humectants, moisturizers, mouth feel agents, colorants, abrasives, preservatives, fluoride ion source, saliva stimulating agents, emollients, viscosity modifiers, diluents, emulsifiers, nutrients and combinations thereof. Various components that may be added to the oral composition include, for example, a sweetening agent such as saccharin, or sodium saccharin, alcohols such as ethanol, fluoride ion sources such as sodium fluoride, as well as glycerine, sorbitol, polyethylene glycols, Poloxomer polymers such as POLOXOMER® 407, PLURONIC® F108, (both available from BASF Corporation), alkyl polyglycoside (APG), polysorbate, PEG40, castor oil, menthol, and the like. It is understood that while general attributes of each of the above categories of materials may differ, there may be some common attributes and any given material may serve multiple purposes within two or more of such categories of materials. Preferably, such carrier materials are selected for compatibility with the active ingredients found in magnolia extract or synthetic analogues thereof, as well as with other ingredients of the composition.

[0022] Flavorants among those useful herein include any material or mixture of materials operable to enhance the taste of the composition. Any orally acceptable natural or synthetic flavorant can be used, such as flavoring oils, flavoring aldehydes, esters, alcohols, similar materials, and combinations thereof. Flavorants include vanillin, sage, marjoram, parsley oil, spearmint oil, cinnamon oil, oil of wintergreen (methylsalicylate), peppermint oil, clove oil, bay oil, anise oil, eucalyptus oil, citrus oils, fruit oils and essences including those derived from lemon, orange, lime, grapefruit, apricot, banana, grape, apple, strawberry, cherry, pineapple, etc., bean- and nut-derived flavors such as coffee, cocoa, cola, peanut, almond, etc., adsorbed and encapsulated flavorants, and mixtures thereof. Also encompassed within flavorants herein are

ingredients that provide fragrance and/or other sensory effect in the mouth, including cooling or warming effects. Such ingredients include menthol, menthyl acetate, menthyl lactate, camphor, eucalyptus oil, eucalyptol, anethole, eugenol, cassia, oxanone, [alpha] -irisone, propenyl guaiethol, thymol, linalool, benzaldehyde, cinnamaldehyde, N-ethyl-p-menthan-3-carboxamine, N,2,3-trimethyl-2- isopropylbutanamide, 3-l-menthoxypropane-l,2-diol, cinnamaldehyde glycerol acetal (CGA), methone glycerol acetal (MGA), and mixtures thereof. One or more flavorants are optionally present in a total amount of 0.01% to 5%, optionally in various embodiments from 0.05 to 2%, from 0.1% to 2.5%, and from 0.1 to 0.5%.

[0023] Sweetening agents among those useful herein include dextrose, polydextrose, sucrose, maltose, dextrin, dried invert sugar, mannose, xylose, ribose, fructose, levulose, galactose, corn syrup, partially hydrolyzed starch, hydrogenated starch hydrolysate, sorbitol, mannitol, xylitol, maltitol, isomalt, aspartame, neotame, saccharin and salts thereof, sucralose, dipeptide-based intense sweeteners, cyclamates, dihydrochalcones, and mixtures thereof.

[0024] Mouth-feel agents include materials imparting a desirable texture or other feeling during use of the composition of the invention.

[0025] Colorants among those useful herein include pigments, dyes, lakes and agents imparting a particular luster or reflectivity such as pearling agents. In various embodiments, colorants are operable to provide a white or light-colored coating on a dental surface, to act as an indicator of locations on a dental surface that have been effectively contacted by the composition, and/or to modify appearance, in particular color and/or opacity, of the composition to enhance attractiveness to the consumer. Any orally acceptable colorant can be used, including FD&C dyes and pigments, talc, mica, magnesium carbonate, calcium carbonate, magnesium silicate, magnesium aluminum silicate, silica, titanium dioxide, zinc oxide, red, yellow, brown and black iron oxides, ferric ammonium ferrocyanide, manganese violet, ultramarine, titaniated mica, bismuth oxychloride, and mixtures thereof. One or more colorants are optionally present in a total amount of 0.001% to 20%, for example 0.01% to 10% or 0.1% to 5%.

[0026] In some embodiments, the oral care compositions of the present invention may comprise an optional abrasive useful for example as a polishing agent. Any orally acceptable abrasive can be used, but type, fineness, (particle size) and amount of abrasive should be selected so that tooth enamel is not excessively abraded in normal use of the composition. Suitable optional abrasives include silica, for example in the form of precipitated silica or as admixed with alumina,

insoluble phosphates, calcium carbonate, and mixtures thereof. Among insoluble phosphates useful as abrasives are orthophosphates, polymetaphosphates and pyrophosphates. Illustrative examples are dicalcium orthophosphate dihydrate, calcium pyrophosphate, calcium pyrophosphate, tricalcium phosphate, calcium polymetaphosphate and insoluble sodium polymetaphosphate.

[0027] In some embodiments, the compositions of the present invention optionally comprise a tartar control (anticalculus) agent. Tartar control agents among those useful herein include salts of any of these agents, for example their alkali metal and ammonium salts: phosphates and polyphosphates (for example pyrophosphates), polyaminopropanesulfonic acid (AMPS), polyolefin sulfonates, polyolefin phosphates, diphosphonates such as azacycloalkane-2,2-diphosphonates (e.g., azacycloheptane-2,2-diphosphonic acid), N-methyl azacyclopentane-2,3-diphosphonic acid, ethane- 1 -hydroxy- 1 , 1 -diphosphonic acid (EHDP) and ethane- 1 - amino- 1, 1-diphosphonate, phosphonoalkane carboxylic acids and. Useful inorganic phosphate and polyphosphate salts include monobasic, dibasic and tribasic sodium phosphates, sodium tripolyphosphate, tetrapolyphosphate, mono-, di-, tri- and tetrasodium pyrophosphates, sodium trimetaphosphate, sodium hexametaphosphate and mixtures thereof.

[0028] In other embodiments, the oral compositions of the present invention optionally comprise a fluoride ion source, useful, for example, as an anti-caries agent. Any orally acceptable fluoride ion source can be used, including potassium, sodium and ammonium fluorides and monofluorophosphates, stannous fluoride, indium fluoride, amine fluorides such as olaflur (N'-octadecyltrimethylendiamine-N,N,N'- tris(2-ethanol)-dihydrofluoride), and mixtures thereof. One or more fluoride ion sources are optionally present in an amount providing a clinically efficacious amount of soluble fluoride ion to the oral composition.

[0029] In further embodiments, the oral compositions of the present invention optionally comprise a saliva stimulating agent useful, for example, in amelioration of dry mouth. Any orally acceptable saliva stimulating agent can be used, including without limitation food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids, and mixtures thereof. One or more saliva stimulating agents are optionally present in saliva stimulating effective total amount.

[0030] In yet other embodiments, the oral compositions of the present invention optionally comprise a nutrient. Suitable nutrients include vitamins, minerals, amino acids, and mixtures

thereof. Vitamins include Vitamins C and D, thiamine, riboflavin, calcium pantothenate, niacin, folic acid, nicotinamide, pyridoxine, cyanocobalamin, para-aminobenzoic acid, bioflavonoids, and mixtures thereof. Nutritional supplements include amino acids (such as L-tryptophane, L-lysine, methionine, threonine, levocarnitine and L-carnitine), lipotropics (such as choline, inositol, betaine, and linoleic acid), and mixtures thereof.

[0031] In some embodiments, the present invention provides a method of treating conditions associated with the presence of oral bacteria comprising providing an oral composition in accordance with any of the above-described embodiments, and applying the oral composition to the oral cavity of the mammalian subject. In some embodiments, the method comprises repeating the application of the composition multiple times until the desired anti -bacterial and/or anti-inflammatory effects are achieved in the subject.

[0032] As referred to herein, "inflammation" of the oral tissue generally refers to a localized protective response elicited by injury or destruction of tissues, which serves to destroy, dilute, or sequester both the injurious agent and the injured tissue. In the acute form, it is characterized by pain, heat, redness, swelling, and loss of function. Chronic inflammation is a slow process and primarily characterized by the formation of new connective tissue. Chronic inflammation is often a continuation of acute inflammation or a prolonged low-grade form of inflammation (such as that associated with periodontitis or gingivitis) and usually causes permanent tissue damage. Histologically, inflammation involves a complex series of events, including dilation of arterioles, capillaries, and venules, with increased permeability and blood flow; exudation of fluids, including plasma proteins, and leukocytic migration into the inflammatory locus. Inflammation corresponds to enhanced levels of proinflammatory cellular mediators, or substances that are released from cells, for example, as the result of the interaction of an antigen with an antibody or by the action of antigen with a sensitized lymphocyte.

[0033] In various embodiments, application or contacting is accomplished by rinsing, coating, brushing, or layering using appropriate dressing materials. In some embodiments, contacting also includes incidental contact during eating or chewing. In various embodiments, application of the composition comprises the use of an application device which aids in maintaining the contact time of the antiinflammatory active ingredient comprising magnolia extract to the target tissue for a sufficient time as to allow the pharmacological inhibition of the elevated production of one or more inflammatory mediators, such as PGE 2 and TNF-alpha.

[0034] In certain embodiments, an oral composition is not intentionally swallowed, but rather is retained in the oral cavity for a time sufficient to effect the intended utility. In other embodiments, particularly those where the oral composition is provided in an animal product, such as a pet food, pet food supplement (e.g., a treat), or a chew toy, the oral composition may be ingested at small concentrations which are not harmful to the animal. Preferably, specific materials and compositions to be used in this invention are pharmaceutically- or cosmetically-acceptable.

[0035] As used throughout, ranges are used as shorthand for describing each and every value that is within the range. Any value within the range can be selected as the terminus of the range. In addition, all references cited herein are hereby incorporated by referenced in their entireties. In the event of a conflict in a definition in the present disclosure and that of a cited reference, the present disclosure controls.

[0036] Unless otherwise specified, all percentages and amounts expressed herein and elsewhere in the specification should be understood to refer to percentages by weight. The amounts given are based on the active weight of the material.

EXAMPLES

Example 1: Compositions

[0037] Compositions with different co-surfactant systems (propylene glycol monocaprylate/SLS, propylene glycol monlaurate/SLS, SLS as sole surfactant) are prepared as follows:

	1	2	3	4
	%	%	%	%
PEG600	2.80	2.80	4.20	2.80
Flavor	1.40	1.40	1.40	1.40
Isobutyl magnolol	1.40	1.40	1.40	
propylene glycol monocaprylate	1.40			
propylene glycol monolaurate		1.40		1.40
Glycerin	25.22	25.22	25.22	25.22
Sorbitol	24.94	24.94	24.94	24.94
Sodium Saccharine	0.42	0.42	0.42	0.42
Sodium Fluoride	0.34	0.34	0.34	0.34
Sodium lauryl sulfate (SLS)	2.10	2.10	2.52	2.52
Water	39.98	39.98	39.55	40.96
Total	**100**	**100**	**100**	**100**

Example 2: Zone of Inhibition Test

[0038] Samples of the four compositions from the preceding example are diluted with water at 0.75:2 and tested for the zone inhibition of *A. viscosus*, using the following protocol:

1. Make the OD610 of A. viscosus at ~0.1
2. Plate 100ul of *A.viscosus* on TSA plate
3. Place 6mm paper disk on the center of TSA plate prepared at step 3
4. Pipet 15ul of slurry to be tested on the paper disk of TSA plate
5. Incubate TSA plate at 37 °C overnight.
6. Measure the zone

	1	2	3	4
Exp. 1 Inhibition zone (cm)	3.04	4.64	2.79	
Exp. 2 Inhibition zone (cm)		4.5		2.13

[0039] It is seen from experiment 1 that the composition comprising isobutyl magnolol in combination with propylene glycol monolaurate (composition 2) is significantly superior to the composition without propylene glycol ester (composition 3), and even to the composition having propylene glycol monocaprylate. Experiment 2 shows that the antibacterial activity is attributable to the combination of isobutyl magnolol and propylene glycol laurate, not to the propylene glycol laurate alone. The composition comprising the isobutyl magnolol and propylene glycol laurate together is greatly superior to compositions comprising one or the other separately.

CLAIMS

1. An oral care composition comprising: isobutyl magnolol; propylene glycol monolaurate; and an orally acceptable carrier; wherein the propylene glycol monolaurate is present in an amount effective to solubilize the isobutyl magnolol in the orally acceptable carrier.
2. The composition of claim 1 in the form of a toothpaste.
3. The composition of claim 1 in the form of a mouthrinse.
4. The composition of any foregoing claim wherein the isobutyl magnolol is present in an antibacterially effective amount.
5. The composition of any foregoing claim wherein the isobutyl magnolol is present in the amount of from about 0.1% to about 3% based on the total weight of the composition.
6. The composition of any foregoing claim wherein the ratio by weight of isobutyl magnolol to propylene glycol monolaurate is from about 0.2:1 to about 2:1.
7. The composition of any foregoing claim wherein the orally acceptable carrier comprises an additional ingredient selected from: polyethylene glycol, a humectant, an anionic surfactant, an effective amount of a fluoride ion source, flavoring, an abrasive, and a combination of two or more thereof.
8. The composition of any foregoing claim comprising the following ingredients by weight:

PEG600	1-4%
isobutyl magnolol	0.5-3%
propylene glycol monolaurate	0.5-3%
glycerin	20-30%
sorbitol	20-30%
sodium saccharine	0.1-0.7%
sodium fluoride	0.1-0.7%
sodium lauryl sulfate	1-3%
abrasive silica	0-20%

9. Use of propylene glycol monolaurate and isobutyl magnolol in combination in the manufacture of an oral care composition for use in a method of treatment, prophylaxis or control of a disease or condition of the oral cavity.
10. The use of claim 9 wherein the disease or condition of the oral cavity is selected from caries, gingivitis, periodontitis, tooth yellowing and halitosis.

11. A method of enhancing the solubility of isobutyl magnolol in an oral care composition comprising admixing a solubilizing effective amount of propylene glycol monolaurate with an orally acceptable carrier comprising isobutyl magnolol.