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(54) Title: ORAL CARE COMPOSITIONS

(57) Abstract: The present oral care compositions can soothe irritated oral mucous membranes, stimulates salivary secretion, and/or freshen breath. The oral care compositions can also be used to prevent and treat mucositis, gingivitis, periodontitis, mouth dryness (xerostomia), oral infections, oral inflammation, and halitosis. The compositions are especially useful in treating oral complications in cancer patients who have undergone chemotherapy or radiation therapy. The present composition contains natural ingredients and may be alcohol-free and/or free of artificial colors.

Oral Care Compositions

Cross Reference to Related Application

This application claims priority to U.S. Provisional Application No. 62/096,080 filed on December 23, 2014, which is incorporated herein by reference in its entirety.

Field of the Invention

The present invention relates to oral care compositions. In particular, the present invention relates to mouthwash formulations that help prevent and treat oral ulcers in cancer patients having undergone chemotherapy and/or radiotherapy. The oral care compositions can also be used to prevent and treat mucositis, gingivitis, periodontitis, mouth dryness (xerostomia), oral infections, oral inflammation, and halitosis.

Background of the Invention

Cancer patients in general are at risk for various infections as a result of their underlying disease or from treatments. Most cancer treatments, such as chemotherapy and radiation therapy, affect normal tissues as well as tumor cells, and are associated with adverse side effects. For example, among the approximately one million people in the United States who are diagnosed with cancer annually, over 400,000 individuals suffer oral complications from their cancer therapies. Oral health in America: a report of the Surgeon General (executive summary), 2014, National Institute of Dental and Craniofacial Research. The oral complications of cancer therapies are, at a minimum, painful and, at their most severe, life threatening. These oral side effects, particularly in patients undergoing chemotherapy and radiation therapy, include mouth ulcers, mucositis, osteoradionecrosis, candidiasis, stomatitis, sore throat, changes in taste sensation, dysphagia, tooth hypersensitivity and rampant dental caries, as well as secondary infections such as herpes. Sometimes the oral ulcers are so painful and severe that patients opt to take a break from treatments, which can make the treatments less effective. These side effects also cause a variety of symptoms which may discourage eating. Therefore, malnutrition and unhealthy weight loss are common consequences of the oral complications. U.S. Patent Nos. 7,128,898 and 5,886,054.

Additionally, patients who have had radiation treatment of the oral cavity or throat are often no longer capable of producing sufficient saliva, because their salivary glands have been entirely or partially destroyed by the radiation treatment. Dry mouth (xerostomia) also occurs regularly in users of certain medications, particularly sedatives, beta-blockers, anti-hypertension medications, tranquilizers and other medicines which have the side effect of dulling the nervous system. In addition to the accompanying discomfort and irritation, a shortage of saliva can result in inflammations of the mouth.

There are no reliable remedies for the cancer treatment related oral complications. While mouthwash is essential for maintaining oral hygiene of such patients, the currently available mouthwash formulations are simply too irritant to cancer patients' sensitive oral mucosa. Therefore, there is a need for effective, gentle oral care compositions to prevent and treat oral complications in cancer patients.

Summary

The present application provides for an oral care composition that may be a mouthwash, a toothpaste, an oral gel or a dental powder.

The composition may comprise (or consist essentially of, or consist of): an *Aloe vera* extract (e.g., an *Aloe vera* leaf extract), a gluconate, a citrate, hydrogen peroxide, a *Matricaria chamomilla* (chamomile) extract, and a cranberry extract (e.g., a cranberry fruit extract). The composition may be alcohol-free or may contain alcohol. The composition may further comprise a zinc ion source, such as zinc gluconate, zinc citrate, zinc acetate, zinc glycinate, zinc oxide, zinc sulfate, sodium zinc citrate, or combinations thereof.

Other additives may be present in the present composition, including, but not limited to, a flavoring agent, such as *Mentha piperita* oil (peppermint oil), *Cinnamomum cassia* oil (cinnamon oil), or a combination thereof; a sweetener, such as a stevia extract; a surfactant, such as a polysorbate (e.g., polysorbate 20); or any combination thereof.

The present application also provides for an oral care composition consisting essentially of (or comprising, or consisting of): water, an *Aloe vera* extract, zinc gluconate, zinc citrate, hydrogen peroxide, a *Matricaria chamomilla* (chamomile) extract, a cranberry extract, at least one surfactant (e.g., polysorbate 20), at least one flavoring agent (e.g., *Mentha piperita* oil (peppermint oil), *Cinnamomum cassia* oil (cinnamon oil), or a combination thereof), and at least one sweetener (e.g., a stevia extract).

The present application further provides for an oral care composition comprising (or consisting essentially of, or consisting of): about 80 – about 98 wt% water, about 0.2 – about 5 wt% *Aloe vera* leaf extract (200:1 solution), about 0.2 – about 5 wt% zinc gluconate (dihydrate), about 0.01 – about 1 wt% zinc citrate, about 0.5 – about 5 wt% of 50% hydrogen peroxide, about 0.1 – about 2 wt% *Matricaria chamomilla* (chamomile) extract (1% solution), about 0.001 – about 0.5 wt% cranberry fruit extract, about 0.01 – about 0.5 wt% surfactant(s), about 0.001 – about 0.5 wt% flavoring agent(s), and about 0.01 – about 0.8 wt% sweetener(s); wherein the weight percentages are based on the total oral care composition.

The composition may contain a preservative, such as sodium benzoate.

The present application also provides for an oral care composition consisting essentially of (or comprising, or consisting of): about 90 – 95 wt% water, about 1 wt% *Aloe vera* leaf extract

(200:1 solution), about 1 wt% zinc gluconate (dihydrate), about 0.2 wt% zinc citrate, about 2 wt% of 50% hydrogen peroxide, about 0.5 wt% of *Matricaria chamomilla* (chamomile) extract (1% solution), about 0.01 wt% cranberry fruit extract, about 0.1 wt% polysorbate 20, about 0.01 wt% *Cinnamomum cassia* oil (cinnamon oil), about 0.01 wt% *Mentha piperita* oil (peppermint oil), about 0.1 wt% stevia extract, and about 0.6 wt% sodium benzoate, wherein the weight percentages are based on the total oral care composition.

Also encompassed by the present application are methods of improving or maintaining oral hygiene, or treating or preventing oral ulcers, oral infection or oral inflammation. The method includes the step of applying the present oral care composition.

Brief Description of the Figures

Figure 1 shows the numbers of patients suffering from various symptoms before and after the mouthwash treatment.

Figure 2 shows an exemplary patient questionnaire to evaluate symptoms associated with xerostomia and mucositis before and/or after the mouthwash treatment.

Detailed Description

The present oral care compositions can soothe irritated oral mucous membranes, stimulate salivary secretion, and/or freshen breath. The oral care compositions can be used to prevent and treat mucositis, gingivitis, periodontitis, mouth dryness (xerostomia), oral infections, oral inflammation, and halitosis. The compositions are especially useful in treating oral complications of cancer patients who have undergone chemotherapy or radiation therapy. The oral compositions can be in the form of a mouthwash or oral rinse; a mouth spray; a dentifrice, including toothpaste, dental gels, dental powder; chewing gum; or a biofilm. Applied to one or more oral surfaces in the oral cavity, the compositions can provide multiple oral care benefits simultaneously and promote overall oral health.

The present composition may be alcohol-free or may contain one or more alcohol. The composition may be free of artificial colors or may contain an artificial color(s).

The natural ingredients of the present oral care composition, such as botanicals, make it effective but gentle enough for daily use in cancer patients with sensitive oral mucosa or in healthy subjects.

In certain embodiments, the oral compositions may also be in the form of animal or pet care products.

Composition

The oral care composition may take the form of a liquid, paste, gel, powder, film or the like. The present oral care composition may comprise (or consist essentially of, or consist of): *Aloe vera* extract, a gluconate, a citrate, hydrogen peroxide, *Matricaria chamomilla* (chamomile) extract, and cranberry extract.

The present composition may contain a natural ingredient for providing a soothing effect to the mouth, such as *Aloe vera* extract or gel, *Matricaria chamomilla* (chamomile) oil or tea, propolis, extract of goldenseal, extract of calendula, extract of bloodroot, menthol, extract of *Piper cubeba*, extract of *Glycyrrhiza glabra*, extract of *Acorus calamus*, extract of *Alpinia galanga*, grapefruit seed extract, extract of oregano, extract of echinacea, extract of Lithospermi radix (gromwell), extract of Artemisia princeps (mugwort), extract of Phellodendri cortex

(phellodendron bark), extract of Moutan cortex (moutan bark), extract of Sctellariae radix (scutellaria root), extract of Rhei rhizoma (rhubarb) and extract of Chrysanthemum indicum (wild chrysanthemum), or combinations thereof.

Such natural ingredients may aid in soothing the gums and mouth tissue, protecting the mouth from irritants and relieving pain or discomfort.

Herbal extracts suitable for use in the present invention can be obtained from any part of a plant including, but not limited to, the leaf, flower, stem, stalk, bark, pulp, seed, flesh, juice, root and mixtures thereof. As used herein, the term "extract" also encompasses synthetic or semi-synthetic equivalents of such a natural extract or an active component thereof. The extracts may be in liquid or dried powder forms.

The present composition may contain an antiseptic, including, but not limited to, *Mentha piperita* (peppermint) oil, *Matricaria chamomilla* (chamomile) oil or tea, extract of echinacea, extract of bloodroot, tea tree oil, extract of wild bergamot, extract of myrrh, extract of Rhatany bark, extract of calendula, or combinations thereof.

The oral composition may comprise an orally acceptable zinc ion source useful, for example, as an antimicrobial, anti-calculus or breath-freshening agent. Suitable zinc ion sources include, without limitation, zinc acetate, zinc citrate, zinc gluconate, zinc glycinate, zinc oxide, zinc sulfate, zinc chlorite, sodium zinc citrate and the like. One or more zinc ion sources are optionally and illustratively present in a total amount of about 0% to about 10%, about 0.001% to about 8%, about 0.005% to about 5%, about 0.001% to about 3%, about 0.01% to about 2%, about 0.1% to about 1.5%, or about 0.1% to about 1%, by weight of the composition.

The present oral composition may also include other additives which may be orally used, such as solvents, flavoring agents, sweeteners, surfactants, pH regulators, preservatives, solubilizing agents, stabilizing agents, viscosity modifiers, diluents, abrasives, humectants, emollients, and moisturizers, chelating agents, coloring agents, binders, lubricants, thickening agents, medical components, and combinations thereof. A solvent having good biocompatibility such as water, ethanol or isopropanol may be used. Non-limiting medical components that may be added to the present composition include antimicrobial (e.g., antibacterial, antifungal, antiviral, etc.) agents, anti-inflammatory agents, immunosuppressive agents, anti-caries agents,

tartar control agents, tooth desensitizers, salivary stimulants, antiplaque agents, and combinations thereof.

It is understood that while general attributes of each of the above categories of additives may differ, there may be some common attributes, and any given material may serve multiple purposes within two or more of such categories of additives.

The present composition may or may not contain a flavoring agent. The flavoring agent can be a terpene, such as the terpene hydrocarbons and oxygenated derivatives thereof, include such compounds as dl-limonene, menthol, diterpenes, polyterpenes and derivatives thereof, many of which are found in various essential oils and other flavors. Suitable flavoring agents can be natural and synthetic oils. The flavoring agents include, for example, *Mentha piperita* (peppermint) oil, *Matricaria chamomilla* (chamomile) oil or tea, menthol, spearmint oil, orange oil, lemon oil, bay oil, citrus oil, lime oil, eucalyptus oil, mentha oil, acacia oil, fennel oil, bitter almond oil, calamus oil, camphorate oil, cassia bark oil, cinnamon leaf oil, rose oil, sandalwood oil, clove oil, wintergreen oil, sassafras oil, sage oil, mint oil, marjoram oil, grape oil, cherry oil, herbal oil, banana oil, apple oil, methyl salicylate, carvone, anethole and limonene.

The total weight percentage of a flavoring agent(s) may be about 0 to about 10%, about 0.001 to about 10%, about 0.001 to about 0.5%, about 0.1 to about 0.5%, about 0.005 to about 5%, about 0.005 to about 2%, about 0.01 to about 2%, about 0.2 to about 3%, about 0.2 to about 1.5%, about 1 to about 2%, about 0.01 to about 1%, or about 0.01 to about 0.5% of the total composition.

The present composition may or may not contain a sweetener. The sweeteners may include, for example, stevia extract, hydrogenated starch hydrolysate, saccharin, sodium saccharate, xylitol, stevioside, revaudioside, p-methoxy cinnamic aldehyde, neohesverisyl hydroxy carcon, perillartine, thaumatin, glycyrrhizin, monoglucoside glycyrrhizinate, hernandulcin, trehalose, aspartame, sorbit, sucrose, lactose, maltose, sorbitol, sodium cyclamate, cyclamates, mannitol, maltitol, and other natural or artificial sweeteners. U.S. Patent No. 6,811,769.

The total weight percentage of a sweetener(s) may be about 0 to about 10%, about 0.01 to about 10%, about 0.01 to about 1%, about 2 to about 7%, about 0.05 to about 5%, about 0.1 to

about 2%, about 0.1 to about 2%, about 0.1 to about 1%, or about 0.1 to about 0.5% of the total oral composition.

The present composition may contain a surfactant. Useful surfactants include suitable anionic, nonionic, cationic and zwitterionic surfactants. Specifically, such agents may include, for example, polysorbates (such as polysorbate 20 which is polyoxyethylene (20) sorbitan monolaurate, polysorbate 40 which is polyoxyethylene (20) sorbitan monopalmitate, polysorbate 60 which is polyoxyethylene (20) sorbitan monostearate, polysorbate 80 which is polyoxyethylene (20) sorbitan monooleate), and polyoxyethylene stearates, polyethoxylated castor oil, an alkyl sulfate, an alkyl benzene sulfonate, a sucrose fatty acid ester, a lactose fatty acid ester, a salt of lauroyl sarcosinc, a salt of N-acyl glutamic acid, sodium lauryl sulfate and other sodium higher alkyl sulfates of 10 to 18 carbon atoms in the alkyl groups thereof, alpha-olefin sulfonate, 2-alkyl-N-carboxy-N-hydroxyethylimidazorium betaine, a salt of N-acyltaurine, alkylol amide, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene hydrogenated castor oil and fatty acid ester thereof, polyglycerin fatty acid ester, sorbitan fatty acid ester, fatty acid ester, polyethylene glycol fatty acid ester, and propylene glycol fatty acid ester. Specific nonionic surfactants include block copolymers of polyoxyethylene and polyoxypropylene.

The total weight percentage of a surfactant(s) may be about 0 to about 10%, about 0.01 to about 5%, about 0.01 to about 0.5%, about 0.01 to about 1%, about 0.05 to about 3%, about 0.1 to about 2%, about 0.1 to about 2%, about 0.0005 to about 0.1%, about 0.1 to about 0.5%, about 1 to about 20%, or about 5 to about 10% of the total oral composition.

The present composition may or may not contain a humectant, such as a polyol, including glycerol, propylene glycol, diethylene glycol, etc.

The present composition may or may not contain one or more preservative. Non-limiting examples of preservatives include, for example, benzoic acid, benzoates such as sodium benzoate; p-hydroxybenzoates such as methyl paraben, ethyl paraben, butyl paraben, isopropyl paraben and propyl paraben; alkyl-diaminoethyl glycin hydrochloride, phenoxy ethanol, sorbic acid, and any combination thereof.

The present composition may have a pH of about 4.5 to about 10, about 5.5 to about 8, about 5 to about 6, about 6 to about 8, or about 5.5.

The pH regulators may include, for example, organic acids such as citric acid, malic acid,

phosphoric acid and acetic acid and salts thereof; sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium carbonate, potassium hydrogen carbonate, calcium carbonate, calcium hydrogen carbonate, ammonium carbonate, ammonium hydrogen carbonate, potassium sodium carbonate, lithium carbonate, urea, disodium phosphate; calcium salts of inorganic acids such as calcium nitrate, calcium sulfate, and calcium glycerophosphate; calcium salts of organic acids such as calcium lactate, calcium acetate, calcium malonate, calcium citrate, calcium gluconate, calcium glycerinate, calcium tartrate and calcium phytate.

The composition may contain vitamins and nutritional supplements, such as such as vitamin A, vitamin C, vitamin E, vitamin B6, pantothenate, or derivatives thereof.

Anti-oxidants may be used in the formulations of the present invention, such as rosemary extract, butylated hydroxtmethyl phenol (BHA) and ascorbic acid (vitamin C).

Non-limiting examples of chelating agents include disodium EDTA.

The composition may contain a solubilizing agent, such as an ester of an unsaturated fatty acid, e.g., ethyl linoleate.

For dentifrice such as toothpaste, bases usable to make the oral composition of the present invention, including, for example, edible oils, silica, calcium carbonate, dental dibasic calcium phosphate and hydroxyapatite.

Binders which may impart viscosity to the oral composition of the present invention include, for example, Xanthan gum, cellulose gum, Carrageenan, polyvinyl pyrrolidone and sodium alginate.

Lubricants may include, for example, sugar alcohols such as sorbitol, maltitol, xylitol and lactitol; and polyhydric alcohols such as glycerin, 1,3-butyleneglycol, 1,2-pentanediol, polyethylene glycol, polypropylene glycol and dipropylene glycol.

The thickening agents may include, for example, carboxy vinyl polymer, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, Carrageenan, alkali metal salts of alginic acid such as sodium alginate; gums such as gellan gum, xanthan gum, cyamoposis gum, tragacanth gum, karaya gum, aluminum magnesium silicate and gum arabic; polyvinyl alcohol, polyvinyl pyrrolidone, silica gel and aluminum silica gel.

The present composition may or may not contain an anesthetic or analgesic, such as a

local anesthetic. Non-limiting examples include clove oil, chamomilla 3XHPUS, benozocaine, belladonna 3XHPUS. U.S. Patent Nos. 8,728,446 and 5,547,657.

The invention can also contain medical components such as antimicrobial (e.g., antibacterial, antifungal, antiviral, etc.) agents, anti-inflammatory agents, antibiotics, immunosuppressive agents, anti-caries agents, tartar control agents, tooth desensitizers, salivary stimulants, antiplaque agents, and combinations thereof. In certain embodiments, an oral care composition of the present invention has more than one active agents.

Non-limiting examples of the medical components include, lysozyme, lactoperoxidase, lactoferrin, allantoin, tocopherol acetate, iso-propyl-methyl-phenol, dextrase, chlorophyll, sodium copper chlorophyll, flavonoid, mutanase, amylase, protease, lytic enzymes, superoxide dismutaze, epsilon aminocaproic acid, aluminum allantoin, aluminum chloro-hydroxy-allantoin, dihydro-cholestanol, bisabolol, glycerophosphate, water soluble inorganic phosphorylated compounds; edetic acid, zinc chloride, copper gluconate, chlorhexidine gluconate, copper chloride, polyphosphate, pyrophosphate; amino acids such as glycin, lysine and histidine; sodium chloride, sodium bicarbonate, aluminum lactate, potassium nitrate, sarcosinate; and polyphenol compounds such as catechins.

Antibacterial agents for use in the present invention include any suitable antibacterial compound, antibacterial botanical extracts or active compounds isolated from such extracts. Non-limiting examples of antibacterial natural extracts include those isolated from green or oolong tea, gold thread, cranberry and other Ericaceae family plants, honeysuckle, grape seed, myrobalan, rosemary, east Indian walnut, neem, niruri, and pine bark.

Green tea and oolong tea are isolated from *Camellia sinensis*. Gold thread extracts are obtained from one or more of the following plant families *Annonaceae, Berberidaceae, Menispermaceae, Papaveraceae, Ranunculaceae, Rutaceae, Zingiberaceae, Nadina, Mahonia, Thalictrum spp*. The honeysuckle (*Lonicera ceprifolium*) extracts are obtained from the flower of the honeysuckle plant. In certain embodiments, extracts from plants in the Vaccinium genus are useful as antibacterial natural extracts, such as cranberry (*Vaccinium macrocarpon*). Other natural extracts that are known antimicrobial agents can be found listed in the International Cosmetic Ingredient Dictionary and Handbook, Tenth Ed., 2004.

Hydrogen peroxide is an oxidizing agent. It can kill bacteria, and also has a mechanical

cleansing action when it froths as it comes into contact with debris in mouth. "Mouthwashes, gargles, and dentifrices". British National Formulary, March 2014, BMJ Group and the Royal Pharmaceutical Society of Great Brain 2014.

Other useful antimicrobial agents include non-ionic and anionic agents known to one of skill in the art. Examples of non-ionic agents include substantially water insoluble, noncationic antibacterial agents. For example, such antibacterial agents include an alkylphenoxy phenol; a cycloalkyl-phenoxyphenol; a 9,10-dihydrophenanthrenol; an alkylphenol; a cycloalkyl-phenol; a phenolic compound; a halogenated carbanilide; a halogenated salicylanilide; a benzoic ester; a halogenated diphenyl ether, and mixtures thereof.

The phenolic compounds may include phenol and its homologs, mono and polyalkyl and aromatic halophenols, resorcinol and its derivatives, and bisphenolic compounds. Non-limiting examples of phenolic compounds include n-hexyl resorcinol and 2,2'-methylene bis(4-chloro-6-bromophenol).

Exemplary halogenated carbanilides, halogenated salicylanilides and benzoic esters are disclosed in U.S. Patent No. 5,776,435. Halogenated carbanilides include 3,4,4'-trichlorocarbanilide, 3-trifluoromethyl-4,4'-dichlorocarbanilide, and 3,3',4-trichlorocarbanilide. Halogenated salicylanilides include 4'5-dibromosalicylanilide, 3,4',5-trichlorosalkylanilide, 3,4',5-tribromosalicylanilide, 2,3,3',5-tetrachlorosalicylanilide, 3,3',5-tetrachlorosalicylanilide, 3,5-dibromo-3'-trifluoromethyl salicylanilide, 5-n-octanoyl-3'-trifluoromethyl salicylanilide, 3,5-dibromo-4'-trifluoromethyl salicylanilide, 3,5-dibromo-3'-trifluoro methyl salicylanilide (Fluorophene), and mixtures thereof. Benzoic esters include methyl-p-hydroxybenzoic ester, ethyl-p-hydroxybenzoic ester, propyl-p-hydroxybenzoic ester, and butyl-p-hydroxybenzoic ester.

Examples of anti-bacterial agents also include, but are not limited to, a diphenyl ether such as 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan) and 2,2'-dihydroxy-5,5'-dibromodiphenyl ether; cetyl pyridinium chloride; benzalkonium chloride; methylbenzethonium chloride; and chlorhexidine gluconate. U.S. Patent Nos. 8,383,171; 6,890,961 and 5,273,741.

In addition to the above described antibacterial agents, which can prevent plaque formation, another embodiment of the composition may comprise an orally acceptable antiplaque agent. An antiplaque agent can operate by an anti-adhesion mechanism, plaque disrupting

mechanism, etc. Additional suitable antiplaque agents include, without limitation, glucose oxidase, stannous salts, copper salts, magnesium salts and strontium salts, dimethicone copolyols such as cetyl dimethicone copolyol, papain, glucoamylase, urea, calcium lactate, calcium glycerophosphate, strontium polyacrylates, citric and tartaric acids and alkali metal salts thereof.

The composition may contain an anti-caries agent, such as a fluorine-containing compound. Useful anti-caries agents include inorganic fluoride salts, such as soluble alkali metal salts. Examples include sodium fluoride, stannous fluoride, potassium fluoride, potassium stannous fluoride (Sn_2KF), sodium hexafluorostannate, stannous chlorafluoride, sodium fluorozirconate, sodium monofluorophosphate (MFP), sodium fluosilicate, aluminum fluoride, silver fluoride, hexyl amine hydrofluorate, decanol amine hydrofluorate, oleyl amine hydrofluorate, ammonium fluorosilicate, and amine fluorides, including olaflur (N'-octadecyltrimethylendiamine-N,N,N'-tris(2-ethanol)-dihydrofluoride). Tin based compounds, including stannous fluoride and stannous chloride are also useful herein.

In various embodiments, the oral compositions of the present invention comprise anti-tartar agents to prevent and/or minimize calculus formation. Suitable anti-tartar agents include without limitation: phosphates and polyphosphates. Inorganic phosphate and polyphosphate salts may include, without limitation, monovalent cations with monobasic, dibasic and tribasic phosphates; tripolyphosphate and tetrapolyphosphate; mono-, di-, tri- and tetra-pyrophosphates; and cyclophosphates (also known as metaphosphates). Useful monovalent cations of such phosphate salts include hydrogen, monovalent metals including alkali metals, and ammonium, for example.

Non-limiting examples of anti-tartar agents include sodium tripolyphosphate or STPP, tetraalkali metal pyrophosphate salts such as tetrasodium pyrophosphate or TSPP, tetrapotassium pyrophosphate, disodium dipotassium pyrophosphate, disodium dihydrogen pyrophosphate, dipotassium dihydrogen pyrophosphate, sodium hexametaphosphate and sodium trimetaphosphate. Other suitable tartar control agents include polyaminopropanesulfonic acid (AMPS), zinc citrate trihydrate, polypeptides such as polyaspartic and polyglutamic acids, 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 salts of any of these agents, for example their alkali metal and ammonium salts.

In one embodiment, the oral composition comprises an orally acceptable stannous ion source useful, for example, in helping reduce gingivitis, plaque, calculus, caries or sensitivity. One or more such sources can be present. Suitable stannous ion sources include, without limitation, stannous fluoride, other stannous halides such as stannous chloride dihydrate, stannous pyrophosphate, organic stannous carboxylate salts such as stannous formate, acetate, gluconate, lactate, tartrate, oxalate, malonate and citrate, stannous ethylene glyoxide and the like.

In another embodiment, the composition comprises an orally acceptable sialagogue (saliva stimulating agent) useful for example in amelioration of dry mouth. One or more of such agents can be present in a saliva stimulating effective amount. Suitable sialagogues include without limitation food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids.

The composition may contain an orally acceptable anti-inflammatory agent. Suitable anti-inflammatory agents include, without limitation, steroidal agents such as flucinolone and hydrocortisone, and nonsteroidal agents (NTHEs) such as ketorolac, flurbiprofen, ibuprofen, naproxen, indomethacin, diclofenac, etodolac, indomethacin, sulindac, tolmetin, ketoprofen, fenoprofen, piroxicam, nabumetone, aspirin, diflunisal, meclofenamate, mefenamic acid, oxyphenbutazone and phenylbutazone.

The present composition may also contain DGL (de-glycyrrhizinated licorice), or chia powder.

Formulation

An oral care composition (e.g., a mouthwash) may comprise (or consist essentially of, or consist of) one or more of the following ingredients in the following weight percentages of the total oral care composition:

(i) deionized, distilled or purified water: about 50 to about 98%, about 60 to about 98%, about 70 to about 98%, about 70 to about 95%, about 80 to about 98%, or about 90 to about 98%;

(ii) *Aloe vera* leaf extract (200:1 solution): about 0 to about 10%, about 0.1 to about 10%, about 0.2 to about 8%, about 0.2 to about 5%, about 0.5 to about 2%, or about 1 to about 2%;

(iii) zinc gluconate (dihydrate): about 0 to about 10%, about 0.1 to about 10%, about 0.2 to about 8%, about 0.2 to about 5%, about 0.5 to about 2%, or about 1 to about 2%;

(iv) zinc citrate: about 0 to about 10%, about 0.01 to about 5%, about 0.01 to about 1%, about 0.05 to about 3%, about 0.1 to about 2%, about 0.1 to about 2%, or about 0.2 to about 0.5%;

(v) hydrogen peroxide (50%): about 0 to about 10%, about 0.1 to about 10%, about 0.2 to about 8%, about 0.2 to about 5%, about 0.5 to about 5%, about 0.5 to about 2%, or about 1 to about 2%;

(vi) *Matricaria chamomilla* (chamomile) extract (1% solution): about 0 to about 10%, about 0.01 to about 5%, about 0.05 to about 3%, about 0.1 to about 2%, about 0.1 to about 2%, or about 0.2 to about 0.5%;

(vii) cranberry fruit extract: about 0 to about 10%, about 0.001 to about 5%, about 0.001 to about 0.5%, about 0.005 to about 3%, about 0.005 to about 2%, about 0.01 to about 1%, or about 0.01 to about 0.5%;

(viii) a surfactant(s), e.g., polysorbate 20: about 0 to about 10%, about 0.01 to about 5%, about 0.01 to about 0.5%, about 0.01 to about 1%, about 0.05 to about 3%, about 0.1 to about 2%, about 0.1 to about 2%, about 0.0005 to about 0.1%, about 0.1 to about 0.5%, about 1 to about 20%, or about 5 to about 10%;

(iv) a flavoring agent(s), (e.g., *Mentha piperita* oil (peppermint oil), *Cinnamomum cassia* oil (cinnamon oil), grape oil, etc. or a combination thereof as described herein): about 0 to about 10%, about 0.001 to about 10%, about 0.001 to about 0.5%, about 0.1 to about 0.5%, about 0.005 to about 5%, about 0.005 to about 2%, about 0.01 to about 2%, about 0.2 to about 3%, about 0.2 to about 1.5%, about 1 to about 2%, about 0.01 to about 1%, or about 0.01 to about 0.5%;

(x) a sweetener(s), e.g., stevia extract, hydrogenated starch hydrolysate, xylitol, or combinations thereof as described herein: about 0 to about 10%, about 0.01 to about 10%, about 0.01 to about 1%, about 2 to about 7%, about 0.05 to about 5%, about 0.1 to about 2%, about 0.1 to about 2%, about 0.1 to about 1%, or about 0.1 to about 0.5%;

(xi) a preservative(s), e.g., sodium benzoate: about 0 to about 5%, about 0.01 to about 5%, about 0.05 to about 3%, about 0.1 to about 2%, about 0.1 to about 2%, about 0.01 to about 0.5%, or about 0.2 to about 0.6%;

(xii) a polyol(s), e.g., propylene glycol, glycerol, etc., or combinations thereof as described herein: about 0 to about 10%; about 2 to about 7%; about 1 to about 5%; or about 1 to about 2%;

In connection with the herein listed ranges of percentages of the components, it should be understood that it is not contemplated within the scope of the invention to have all or most of the ingredients present in their respective maximum listed range in any given composition, as such a composition would be incapable of existence for having more than 100% of the sum of its components. Rather, it is contemplated that when one or more ingredients are in their maximum range, then the ratios of other components are in less than their maximum range, so that the sum total of all components (listed or not listed above) is 100%.

In one embodiment, the present composition comprises (or consists essentially of, or consists of) water, Aloe Barbadensis leaf juice (aloe vera extract), zinc gluconate, zinc citrate, hydrogen peroxide, Matricaria Chamomillia (Chamomile extract), cranberry fruit extract, Mentha Peperita oil (peppermint oil), Stevia, Cinnamomum Cassia (cinnamon oil), polysorbate 20, Sodium Benzoate. The composition may or may not contain other flavoring agent(s).

In another embodiment, the present composition comprises (or consists essentially of, or consists of) Peppermint oil, purified water, lysozyme, aloe vera (extract), hydrogenated starch hydrolysate, propylene glycol, zinc gluconate, zinc citrate, calcium lactate, xylitol, glucose oxidase, lactoperoxidase, lactoferrin, cinnamon tea, propolis, chamomile tea, DGL (de-glycyrrhizinated licorice), disodium phosphate, cranberry fruit extract, benzoic acid, and chia powder.

Conditions to be treated

The present compositions may be used to treat oropharyngeal, odontogenic or gingival diseases. The present compositions can be used to treat or prevent oral ulcers, mucositis, stomatitis, oral candidiasis, gingivitis, oral infections, oral inflammation, mouth dryness (xerostomia), and halitosis in a subject. Erythema and eruptions of the mucous membrane may also be treated or prevented. The present compositions may be used to treat or prevent caries, plaque formation, gingivitis and periodontitis. The subject may or may not have been treated with chemotherapy or radiation.

The present compositions may provide beneficial effects on soft tissue and/or hard tissue of the oral cavity, including the gums, soft and hard palates, tongue and mouth floor.

The present composition may be used in the following subjects: cancer patients undergoing radiation therapy and/or chemotherapy (during treatment and/or after treatment); patients suffering from medical conditions in which salivary secretion is reduced or absent (e.g., xerostomia); patients suffering from Sjogren syndrome; patients with decreased salivary secretion resulting from administration of various medications; patients with an impaired immune system; bone marrow transplant patients during and after treatment; patients suffering from graft-versus-host disease; AIDS patients; patients with high susceptibility to dental caries; patients with sensitive teeth, and subjects who wish to promote better oral health and/or maintain oral hygiene. U.S. Patent Nos. 8,404,261 and 6,387,352.

After treatment with the present oral care composition, the unstimulated or stimulated salivary flow rate may increase by greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, greater than 95%, from about 10% to about 10 fold, from about 20% to about 8 fold, from about 50% to about 6 fold, from about 80% to about 5 fold, from about 90% to about 3 fold, from about 10% to about 90%, from about 30% to about 80%, from about 1 fold to about 8 fold, from about 2 fold to about 6 fold, from about 3 fold to about 5 fold, from about 1 fold to about 15 fold or greater, compared with the unstimulated or stimulated salivary flow rate before treatment with the present oral care composition.

A variety of techniques may be used to measure the unstimulated and/or stimulated salivary flow rates. Unstimulated saliva may be collected by spitting any saliva into a sterile, pre-weighed container over a period of time (e.g., 1 minute, 2 minutes, 3 minutes, 5 minutes, or a longer time period). In another embodiment, to measure the unstimulated salivary flow rate, a collection of saliva is drained into a container for a duration of 5-15 minutes. An alternate test to measure unstimulated salivary flow rate is to place a graduated absorbent strip at the floor of the mouth followed by interval readings at 1 minute, 2 minutes, 3 minutes, 4 minutes, 5 minutes or a longer time period. Stimulated saliva may be collected by having the subject chew on a standard piece of sterilized silicone rubber tubing for 5 minutes and spitting all saliva into a sterile, pre-

weighed container. The weight of the unstimulated saliva or stimulated saliva can be recorded and the salivary flow rate determined and expressed as ml/min.

For the measurement of xerostomia, a subjective symptom, a thorough health history, oral examination, drug history, and/or dry mouth questionnaire may be performed. A common reliable questionnaire is the Xerostomia Inventory (XI), an 11-item scale useful for measuring the severity of xerostomia (see, e.g., Table 1).

Table 1

Xerostomia Inventory (Shortened version)						
Complaint		**Never**	**Hardly Ever**	**Rarely**	**Fairly Often**	**Very Often**
1	I sip liquids to help swallow food	1	2	3	4	5
2	My mouth feels dry when eating a meal	1	2	3	4	5
3	I get up at night to drink	1	2	3	4	5
4	My mouth feels dry	1	2	3	4	5
5	I have difficulty in eating dry foods	1	2	3	4	5
6	I suck sweets or cough lozenges to relieve dry mouth	1	2	3	4	5
7	I have difficulty swallowing certain foods	1	2	3	4	5
8	The skin of my face feels dry	1	2	3	4	5
9	My eyes feel dry	1	2	3	4	5
10	My lips feels dry	1	2	3	4	5
11	The inside of my nose feels dry	1	2	3	4	5

After treatment with the present oral care composition, one or more symptoms including, but not limited to, dry mouth, oral ulcer, taste alteration, oral pain, mucosal inflammation, tongue coating, malodor, dysphagia, difficulty eating, difficulty talking, or combinations thereof, may be

reduced by greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, or greater than 95%, compared with the one or more symptoms before treatment with the present oral care composition.

After treatment with the present oral care composition for any time period as described herein, the duration of a condition or symptom (or more conditions or symptoms) may be reduced by greater than 10%, greater than 20%, greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70%, greater than 80%, greater than 90%, or greater than 95%.

Before, during, and/or after treatment with the present oral care composition, a questionnaire to gather subjective information regarding level of pain, nutritional restrictions, dehydration, dryness, and improvement of these symptoms may be answered by the subject. The questionnaire may be completed once, twice, three times, four times, five times, six times, or more times every day, every other day, every three days, at a longer interval, or as needed.

Methods of using the oral care compositions

The present invention also provides for a method of treating or preventing oral ulcers, inflammation or infection in a subject, where the subject's oral cavity surface is contacted with the present oral care composition. Subjects who are immunocompromised, have severe systemic disease or cancer should maintain oral hygiene to control oral complications related to their condition and treatment. Moreover, oral rinsing aids in clearing bacteria from the mouth and throat from healthy individuals. The present methods also can be used to maintain or improve oral hygiene in healthy subjects.

The oral composition may be applied regularly to an oral surface, e.g., on a daily basis, or every second or third day. The oral composition may be applied to the oral surfaces 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times daily. The oral composition may be used for about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 1 month, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 1 year, about 2 years, as long as needed, or more up to lifetime.

The container to store the present composition may be a bottle, a jar, a tube, a packet, a deformable dispensing tube, a pump dispenser, a pressurized dispenser, an oral irrigator or a sachet.

For a mouthwash, the subject rinses first with the mouthwash for about 5 seconds to about 10 minutes, about 10 seconds to about 5 minutes, about 30 seconds to about 2 minutes, about 1 minute, about 10 seconds to about 50 seconds, about 20 seconds to about 40 seconds; and expectorates. The rinse can be repeated once or multiple times. The oral cavity may be further rinsed with water.

For oral irrigation, the composition may be directed toward the desired location in the mouth. The user then expels the excess solution after the rinse has been employed. The user can also squeeze the composition into the mouth from the container until the user has a mouthful of the composition. The composition can be swished within the mouth. To rinse the throat, the user directs the apparatus towards the back of the throat and squeezes the container to force the composition towards the throat. Alternatively, the user can take the composition from a cup or mug. A user who is unable to take the solution on their own can have the solution placed in his or her mouth with an apparatus, such as, for example, a straw or oral syringe. The user can gargle or swish the solution in the mouth or throat, and then expel the composition. Users unable to expel on their own can have the solution suctioned from their mouth and throat with an aspirator. Oral irrigation can be performed at regular intervals to relieve irritation, or discomfort. U.S. Patent Nos. 6,688,497 and 5,145,664.

For a dentifrice, the method of the present invention may include brushing a subject's teeth with a dentifrice such as toothpaste or dental powder. After toothpaste application and brushing is completed, the toothpaste or dental powder is rinsed with water and expectorated.

Dental gel may be applied to the oral cavity surface in general or the oral lesion only. After application, the mouth may be rinsed with water. U.S. Patent No. 6,890,961.

Mouth spray entails spraying the solution into the oral cavity and retaining it for about 5 seconds to about 10 minutes, about 10 seconds to about 5 minutes, about 30 seconds to about 2 minutes, about 1 minute, about 10 seconds to about 50 seconds, or about 20 seconds to about 40 seconds. After that the solution could be safely swallowed or simply expectorated. U.S. Patent No. 8,679,463.

Preparation of the compositions

The oral compositions of the present invention may be prepared by suitably mixing the ingredients.

In one embodiment, in the preparation of a mouthwash, an antibacterial agent is dispersed in a flavor oil and then added to a mixture of humectants, surfactants, and water. The resulting rinse product is then packaged.

In another embodiment, dentifrices are prepared by adding various salts (including fluoride), and sweeteners to water, where it is mixed. Into another container, all humectants, gums, and polymers are added together. The water mixture described above is added to the container with the humectants, gums, and polymers. The combined ingredients are optionally heated to about 140 to about 160°F to disperse the gums and polymers. The heated mixture is then cooled to less than approximately 100°F. The mixture is then combined with abrasives, where it is mixed at high speed under vacuum for 15 to 20 minutes. The flavor oil and active ingredient is then added to the mixture and mixed under high speed and vacuum until sufficiently dispersed. Surfactants are added and the mixture is again mixed to disperse.

Where the oral composition is in the form of a film, it can be formed by any number of conventional film forming processes, such as conventional extrusion or solvent casting processes. For example, to prepare a film by solvent casting, a film forming polymer is dissolved in a sufficient amount of a solvent which is compatible with the polymer. After a solution has been formed, a plasticizer can be added with stirring, and heat can be applied if necessary to aid dissolution, until a clear and homogeneous solution has been formed, followed by the addition of the active ingredients, surface active agents, bulking agents, and any other ingredients such as flavors and sweeteners. For ease of use, the dry film can be cut into pieces of suitable size and shape and packed into a suitable container.

The oral composition of this invention can be incorporated into confectionery. Such methods of forming confectionery (e.g., gum, lozenges) are well known by one of skill in the art, and can be prepared by stirring the extracts into a warm gum base or coating the outer surface of a gum base (for example, jelutone, rubber latex, vinylite resins, inter alia), desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The following examples of specific aspects for carrying out the present invention are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

EXAMPLES

Example 1 Preparation of mouthwash formulation

A mouthwash composition having the ingredients listed in Table 2 is prepared by the following method.

The mouthwash formulation is prepared by conventional methods. In one embodiment, the mouthwash is prepared by mixing the components under continuous agitation at ambient temperature. Care is taken that each added component is completely dissolved before the next item is added.

Table 2

Ingredient	Percentage
Purified Water	93.47%
Aloe barbadensis leaf extract 200:1 solution	1.00%
Zinc Gluconate (dihydrate)	1.00%
Zinc Citrate	0.20%
50% Hydrogen Peroxide Food Grade	2.00%
Stevia Extract	0.10%
Chamomile Extract, 1% solution	0.50%
Sodium Benzoate	0.60%
Grape Flavor	1.00%
Cinnamon Oil	0.01%
Polysorbate 20	0.10%
Peppermint Oil	0.01%
Cranberry Fruit Extract	0.01%

Example 2 Evaluation of efficacy of mouthwash formulation

A total of 17 patients used the mouth rinse for at least one week. Symptoms associated with xerostomia and mucositis after 1 week of treatment with the mouth rinse were then evaluated. The numbers of patients suffering from various symptoms are reflected in Table 3 and Figure 1.

Table 3

	Before Mouthwash	After Mouthwash	Group response rate-symptom reduction
Dry Mouth	14	3	-78.57%
Oral Ulcer	7	3	-57.14%
Taste Alteration	6	4	-33.33%
Oral Pain	7	4	-42.86%
Mucosal inflammation	5	3	-40.00%
Tongue Coating	2	0	-100.00%
Malodor	5	0	-100.00%
Dysphagia	4	2	-50.00%
Difficulty eating	4	2	-50.00%
Difficulty talking	2	1	-50.00%

Example 3 Two-stage Phase II study evaluating the efficacy of mouth rinse in reducing symptom duration in patients developing xerostomia

This two-stage phase II study will evaluate the efficacy of the mouth rinse in patients who develop xerostomia. Patients will be screened for eligibility prior to receiving oral mouth rinse therapy and, following informed consent, undergo baseline evaluation of oral mucosa status and saliva for levels of salivary flow rate [Pre-treatment evaluation]. Patients who develop xerostomia will undergo evaluation of oral mucosal status and salivary flow rate [Day 1 evaluation]. Patients will be treated with the mouth rinse four (4) times a day for a total of seven

(7) days (Days 1-7). A daily questionnaire to gather subjective information regarding level of pain, nutritional restrictions, dehydration, dryness, and improvement of these symptoms following treatment with the mouth rinse, will be answered by all patients four (4) times a day (Days 1-7) (see Figure 2). After seven (7) days of treatment with the mouth rinse, patients will undergo a final evaluation of oral mucosal status and salivary flow rate [Day 8 evaluation]. Response to the mouth rinse will be defined as: a. more than 50% improvement of xerostomia symptoms and pain as reported on the questionnaire; and b. improvement of xerostomia based on xerostomia questionnaire, by the end of study (Day 8). Levels of salivary flow rate may be used as a parameter to determine response. Continuation and stopping rules for the study will be defined based on efficacy of the intervention using a Simon two-stage phase II design.

Background

Xerostomia is known as the subjective sensation of dry mouth with or without salivary gland hypofunction [1]. It has proven to be a developing issue that is no longer exclusive to the geriatric or oncologic population. With the constant development of pharmaceuticals to treat a variety of conditions, from mental health to diabetes, the treatments come with a consequence that often goes overlooked. Symptoms can vary and often go unnoticed by the patient, general practitioner, and oral healthcare professional. Patients who have suffered from recurrent dental caries or gingivitis are at times overlooked for the evaluation of xerostomia. In general, common complaints mentioned are halitosis, ulceration, inflammation, dysgeusia, dysphagia, difficulty talking, difficulty eating, oral tenderness, and problems with the use of dentures [2]. Patients may present sticking of the tongue or buccal mucosa, frothy saliva, no saliva pooling, caries, or debris on palate [3].

The prevalence of xerostomia can vary from 10-47% depending on the population [2,3]. It has undoubtedly shown to be a common issue with increasing age affecting roughly 30% of people over 65 years old [4]. Naturally the aging individual has a higher risk of developing symptoms largely due to the daily use of multiple medications with at least one decreasing the salivary flow rate or causing xerogenic effects [5]. Moreover, treatment is likely for a medical condition associated with salivary hypofunction. Dry mouth symptoms were shown to be 80% of the most frequent oral side effect when 200 commonly prescribed medications were evaluated

for drug-related effects [6]. The most common medications associated with xerostomia are cytotoxic drugs, hypoglycemics, antihistamines, diuretics, beta blockers, antipsychotics, antidepressants, atropinics, non-steroidal anti-inflammatory drugs, steroid inhalers, opioids, thyroid replacements, and anticoagulants [5,6]. When a xerogenic drug is used it can inhibit the normal functions that occur within the autonomic nervous system. The transmission of signals is inhibited at the parasympathetic neuroeffector and adrenergic neuroeffector junctions leading to failure of stimulating salivary gland secretion [7].

A number of systemic diseases and psychological disorders have contributed to the prevalence of xerostomia including diabetes, depression, anxiety, bulimia, nutritional deficiencies, rheumatoid arthritis, Sjorgren's syndrome, and infectious diseases. These diseases and conditions directly affect salivary glands and cause decreased salivary production [8]. A meta-analysis analyzing the prevalence of xerostomia in persons with diabetes mellitus was reported at 42.2% [9]. Flow rates of the parotid gland were also found to be significantly low in poorly controlled diabetes [10]. When evaluating the differences between gender, women are more likely to develop dry mouth symptoms. Mouth breathing brought on by full or partial obstruction of the upper airway can be a problem for a person of any age [11]. When mouth breathing is experienced for long periods of time, the lack of moisture can predispose a person to the development of dental caries and gingivitis. Research has linked the consumption of caffeinated beverages and alcohol to the developing condition. Smokers are another vulnerable population at high risk for xerogenic effects. A preliminary study, evaluating the association of xerostomia among smokers, showed that the prevalence of xerostomia in smokers was 37% [12]. Xerostomia and hyposalivation are the predominant complication and side effect of head and neck cancer (HNC) patients treated with radiation-therapy and/or chemotherapy. There is a nearly 100% chance for these patients to develop symptoms [7]. According to several studies, radiation dosages of at least 20 Gy can stop salivary flow. Doses above 50 Gy are known to destroy malignant cells which often lead to chronic xerostomia [13]. Some hypothesize this includes direct damage to salivary gland cell's DNA by way of radiation-induced reactive oxygen species [10].

Saliva plays an important role for the mucosal immune system by maintaining the right environment within the oral cavity. Antimicrobial substances including lysozyme, lactoferrin,

peroxidases, and antifungal histatins can be found in saliva [13]. The functions of saliva are to maintain normal pH balance, provide antimicrobial protection, debride and lubricate the mucosa. When any or all of these functions fail to work properly the mucosal barrier weakens and integrity of tooth enamel is altered. In these conditions the person is susceptible for developing complications consisting of oral mucositis, oral candidiasis, periodontal disease, and caries [14]. On average the normal unstimulated salivary flow rate is 0.3 mL/min and a normal stimulated flow rate is around 1 to 2 mL/min [15]. A variety of techniques are used to measure salivary flow rates. To measure unstimulated salivary flow, a collection of saliva is drained into a container for a duration of 5-15 minutes. This technique may be done in the morning after an overnight fast. An alternate test to measure unstimulated salivary flow is with a graduated absorbent strip which is placed at the floor of the mouth followed by interval readings at 1, 2, and 3 minutes. For the measurement of xerostomia, a subjective symptom, a thorough health history, oral examination, drug history, and dry mouth questionnaire are useful tools. A common reliable questionnaire is the Xerostomia Inventory (XI), an 11-item scale useful for measuring the severity of xerostomia [15].

Many strategies for treating xerostomia have been proposed as more cases developed throughout the years. Each individual treatment is different and is not conclusive to many or one patient. Some easier approaches to less chronic xerostomia include adequate hydration, avoidance of crunchy/hard foods and use of sugar-free chewing gums/candy [16]. Recent sialogogues, agents that stimulate saliva flow, have been approved by the FDA also aid patients with xerostomia [17]. Pilocarpine, a parasympathomimetic medication, uses muscarinic action whereas cevimeline is a salivary gland stimulant with a greater affinity for M3 Muscarinic receptors [18]. The administered dosages daily differ with cevimeline administered at 30mg three times a day for 3 months and Pilocarpine 5mg a day for three months. Some saliva stimulants such as special mouthwashes, gels and toothpastes are also popular and easily accessible to patients with severe dry mouth. These substitutes aim to increase viscosity and mimic natural saliva without changing salivary flow.

Mouth Rinse

In one embodiment, the present mouth rinse is soothing, hydrating, and possess anti-

inflammatory and antimicrobial effects, and have a good safety profile. The present mouth rinse may be a blend of natural, non-irritant botanical extracts, including (comprising, consisting essentially of, or consisting of), e.g., chamomile, aloe, cranberry such as cranberry fruit extract, cinnamon oil, and peppermint extract or oil. The mouth rinse may also include hydrogen peroxide. The mouth rinse may contain the various components as described herein in a purified water solution devoid of alcohol or irritants. The mouth rinse may help persons suffering from xerostomia and other causes of oropharyngeal soreness and ulceration. The mouth rinse may improve the discomfort associated with odontogenic and oropharyngeal inflammation and pain.

The present oral care composition may reduce inflammation affecting the skin and mucous membranes, reduce a multitude of gastrointestinal symptoms including nausea, vomiting, indigestion, anorexia, flatulence, improve wound healing, reduce healing time for a multitude of oral conditions such as oral mucositis (OM), recurrent aphthous stomatitis, and gingivitis, treat infections such as oral candidiasis, reduce oxidative stress, prevent or treat infections and degenerative diseases, prevent oral disease, inhibit adhesions by various bacteria such as infectious pathogens of the urinary tract, Helicobacter pylori and pathogens of oral disease, reduce biofilm formation, reduce adherence of Porphyromonas gingivalis, reduce proteolytic activities, reduce co-aggregation of periodontal pathogens, treat fungal, gram positive and gram negative infections commonly acquired by patients with OM, have antifungal effects against *candida* albicans, or any combination thereof.

We hypothesize that treatment with the present mouth rinse for patients who develop xerostomia will result in reduction of symptom burden and duration.

The objectives include determining the efficacy of the mouth rinse in reducing duration of symptoms and promoting mucosal healing after seven (7) days of treatment in patients with xerostomia. The objectives also include determining the effect of the mouth rinse on levels of salivary flow rate after seven (7) days of treatment.

Study Population

There will be no patient restrictions based on race or gender. All patients must be 18 years of age or older. Up to nine (9) subjects who develop xerostomia may be treated with the present mouth rinse during the first stage of the study. Following continuation rules, up to

seventeen (17) subjects who develop xerostomia may be treated with the mouth rinse at the completion of study.

Eligibility Criteria

Patients must have baseline evaluations performed prior to enrollment and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled on the study unless otherwise specified.

Inclusion criteria include ability to provide informed consent; at least eighteen (18) years of age; willing to provide saliva to determine salivary flow rate; and no history of salivary gland disease.

Exclusion criteria include: (1) patient has history of salivary gland disease; (2) patients with contraindications or allergies to any component(s) of the mouth rinse are excluded; (3) patients with psychological or geographic conditions that prevent adequate follow-up or compliance with the study protocol are excluded; and (4) patients receiving radiotherapy to the head and neck region, myeloablative, cytotoxic and/or immunotherapy other than the specified in the inclusion criteria are excluded from participation.

Reasons for withdrawal of patients from study may include the following. If, at any time, a patient is found to be ineligible for the protocol according to patient inclusion and exclusion criteria, he or she will be removed from the study. Patients will be withdrawn from study in the event of protocol non-compliance. Patients may voluntarily withdraw from study, if they decide to do so, for any reason.

A subject withdrawn by virtue of progressive xerostomia will continue to receive standard care, as medically indicated and at the discretion of his or her physician. All subjects will be requested to adhere to the protocol schedule for clinic visits. Saliva samples will be requested according to the protocol schedule. As far as is reasonable, data will continue to be collected at the indicated protocol time-points.

In the event of screening failures post-enrollment, patients will be replaced. Reasons for

replacement may also include: inability of enrolled subjects to comply with therapy and/or follow-up visits; voluntary withdrawal of subjects prior to initiation of treatment; and failure to tolerate blood draws.

Study Schedule

Pre-treatment evaluations include baseline evaluation of oral mucosal status for clinical trial enrollment; baseline saliva samples to determine salivary flow rate as defined; and initiation of treatment with the mouth wash on day 1. Treatment visits and procedures are listed in Table 4.

Table 4 Study Calendar

PROCEDURE	DAY								
	Pre-TX	1	2	3	4	5	6	7	8
Screening evaluation and Informed consent	X								
Medical History	X								
History & Physical	X								
Karnofsky Performance Status	X								
Levels of salivary flow rate	X	X							X
Concomitant Medications	X								X
Oral mucosal status	X	X							X
Mouth rinse 10-15 mL QID before meals		X	X	X	X	X	X	X	
Patient Daily Questionnaire		X	X	X	X	X	X	X	

Primary Endpoint

The primary endpoint for this two-stage Phase II study is efficacy. Up to nine (9) patients will be enrolled in the first-stage of the study. Early stopping rules will be in place to protect patients from receiving potentially ineffective treatment. If response as defined is observed in one (1) or more of the first nine (9) patients treated, the study will advance to the second stage. Up to seventeen (17) subjects may be treated in the study.

Efficacy Endpoint

The main endpoint of this two-stage Phase II study is efficacy, including improvement of symptoms and mucosal healing related to xerostomia, within a week of treatment with the mouth rinse. Responses will be evaluated in all patients enrolled in the study. During the first stage of the study, up to nine (9) patients with xerostomia will receive the planned treatment with the mouth rinse and response evaluated after one week. If response occurs in one (1) or more of the nine (9) patients treated, the second stage of the study will continue. Otherwise, the study will be halted. With regard to the second stage, the accrual goal will be up to seventeen (17) patients. Stopping criteria will be based on a defined number of responses and will follow a Simon 2-stage design with a null hypothesis of 5% efficacy ($p_0 = 0.05$) and alternative hypothesis of 25% efficacy ($p_1 = 0.25$) with desired significance level (α) and desired power ($1-\beta$) of 0.05 and 0.9, respectively. Analysis of response will be conducted after accrual of nine (9) subjects completing the planned seven (7) days of treatment with the mouth rinse (day 8). If no responses are observed (0/9 patients), early stopping will be considered based on lack of efficacy of the intervention. With this rule, the probability of early termination (if the alternative hypothesis is true) is seven and one half percent (7.5%). If three (3) or more patients, out of a total of seventeen (17) develop a response, as defined, then the null hypothesis of 5% IE can be rejected and results will be deemed favorable to move to a randomized phase II study.

Efficacy Endpoint will be determined as follows: (a) Patients will self-evaluate the severity and duration of xerostomia symptoms using a validated questionnaire four (4) times daily. An improvement of $\geq$ 50% in the severity of symptoms (including pain) based on answers is defined as a response; and (b) the treating physician will assess the patient's oral mucosa at baseline [Pre-treatment evaluation], Day 1 evaluation and after seven (7) days of treatment [Day 8 evaluation] with the mouth rinse. Xerostomia will be graded following the Xerostomia Inventory (See Table 1) and a response defined as decreased reports of oropharyngeal complaints on Day 8.

Reasons for discontinuation of study include lack of response during stage 1 (first 9 patients).

Screening Visits and Procedures

Screening evaluations will include the following: a) history and physical examination; b)

Karnofsky performance status (see Table 5); c) Baseline evaluation of oral mucosal status for clinical trial enrollment; and d) Baseline saliva samples to determine salivary flow rate.

Table 5 Karnofsky Performance Status Scale

DEFINITIONS	RATING (%)	CRITERIA
Able to carry on normal of activity and to work; No special care needed.	100	Normal no complaints; no evidence disease.
	90	Able to carry on normal activity; Minor signs or symptoms of disease.
	80	Normal activity with efforts; some signs or symptoms of disease.
Unable to work; able to live at normal home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; Requires equivalent of institutional or hospital care; diseases may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; Active supportive treatment necessary.

10	Moribund; fatal processes progressing rapidly.
0	Dead

Study Visits and Procedures

See Table 6 for the mouth rinse treatment schedule.

Table 6 Mouth Rinse Treatment Schedule

Day 1 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 2 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 3 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 4 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 5 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 6 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 7 mouth rinse 10-15ml (or 5-15ml) PO QID	Day 8 10 Response Evaluation

Treatment with the mouth wash will be initiated on day 1. Salivary flow rate will be obtained at the time of enrollment (Pre-treatment), Day 1 and after seven (7) days of treatment with the mouth rinse (Day 8).

Sample Collection

The salivary flow will be measured for all patients included in the study. Samples of unstimulated salivary flow will be collected in graduated millimeter tubes. In order to obtain a clean sample a mouthwash of water is used to gargle and eliminate any possible debris in the mouth. The patient was then instructed to deposit all the saliva accumulated over a period of 5 minutes into the tube.

Salivary samples for unstimulated modified salivary test (MST) may be performed between 8 AM to 12PM prior to eating and drinking, or 2 hours after eating and drinking. Collection of saliva is recommended to be done with patient sitting upright. The patient will raise tongue to have test strip placed on the floor of the mouth. Depending on the length of wetting, readings will be recorded immediately at 1 minute, 2 minutes and 3 minutes intervals. A reading of <25mm will be suggestive of hyposalivation.

Response to the mouth rinse will be evaluated after seven (7) days (Day 8) of treatment

following onset, as previously defined.

Treatment

Patients enrolled on study and who develop xerostomia, as defined, will be treated with the mouth rinse at a dose of 10-15 mL (or 5-15 mL) orally four times a day. Patients will be instructed to swish with the mouth rinse for at least 20-30 seconds and then spit rinse.

If one (1) or more of the first nine (9) patients treated develop a response as described, the second stage of the study will proceed. Up to seventeen (17) patients will be treated in the study for evaluation clinical response.

Immunosuppressive or anti-inflammatory drugs (including hydrocortisone) that inhibit cellular immune responses should be reported. All medications (prescription and over the counter), vitamin and mineral supplements, and/or herbs taken by the study subjects will be documented. Use of oral paste steroids is not permitted.

Subjects will be given a checklist for daily recording of health status, pain, treatment side effects, and documentation of all other medications and dietary supplements that may be taken.

Sample Size

An initial cohort of up to nine (9) subjects will receive treatment with the mouth rinse for xerostomia symptoms. Depending on the response rate during the initial stage, additional patients will receive treatment (up to seventeen (17)) for evaluation of response.

Statistical Methods

A Simon 2-stage design with a null hypothesis of 5% IE ($p_0 = 0.05$) and alternative hypothesis of 25% IE ($p_1 = 0.25$), with desired significance level (α) and desired power ($1-\beta$) of 0.05 and 0.9, respectively, will be utilized. An analysis of response will be conducted after accrual and treatment of the first nine (9) patients, following completion of the planned seven (7) days of treatment. If no responses are observed at interim analysis, the study will be stopped based on lack of efficacy. If 1 or more responses are observed in the first 9 patients treated the study will continue with accrual and treatment of a total of seventeen (17) patients. The probability of early termination, if no responses are observed in the first nine (9) patients, and the

alternative hypothesis is true, is 7.5%. If 3 or more responses out of a total of 17 patients are observed, the null hypothesis can be rejected and the mouth rinse may move to a formal randomized Phase II study.

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The scope of the present invention is not limited by what has been specifically shown and described hereinabove. Those skilled in the art will recognize that there are suitable alternatives to the depicted examples of materials, configurations, constructions and dimensions. Numerous references, including patents and various publications, are cited and discussed in the description of this invention. The citation and discussion of such references is provided merely to clarify the description of the present invention and is not an admission that any reference is prior art to the invention described herein. All references cited and discussed in this specification are incorporated herein by reference in their entirety. Variations, modifications and other implementations of what is described herein will occur to those of ordinary skill in the art without departing from the spirit and scope of the invention. While certain embodiments of the present invention have been shown and described, it will be obvious to those skilled in the art that changes and modifications may be made without departing from the spirit and scope of the invention. The matter set forth in the foregoing description and accompanying drawings is offered by way of illustration only and not as a limitation.

What is claimed is:

1. An oral care composition comprising: an *Aloe vera* extract, a gluconate, a citrate, hydrogen peroxide, a *Matricaria chamomilla* (chamomile) extract, and a cranberry extract.

2. The composition of claim 1, wherein the composition is alcohol-free.

3. The composition of claim 1, further comprising a zinc ion source.

4. The composition of claim 3, wherein the zinc ion source is zinc gluconate, zinc citrate, zinc acetate, zinc glycinate, zinc oxide, zinc sulfate, sodium zinc citrate, or combinations thereof.

5. The composition of claim 1, wherein the *Aloe vera* extract is an *Aloe vera* leaf extract.

6. The composition of claim 1, wherein the cranberry extract is a cranberry fruit extract.

7. The composition of claim 1, wherein the gluconate is zinc gluconate.

8. The composition of claim 1, wherein the citrate is zinc citrate.

9. The composition of claim 1, further comprising a flavoring agent.

10. The composition of claim 9, wherein the flavoring agent is *Mentha piperita* oil (peppermint oil), *Cinnamomum cassia* oil (cinnamon oil), or a combination thereof.

11. The composition of claim 1, further comprising a sweetener.

12. The composition of claim 11, wherein the sweetener is a stevia extract.

13. The composition of claim 1, further comprising a surfactant.

14. The composition of claim 13, wherein the surfactant is a polysorbate.

15. The composition of claim 14, wherein the polysorbate is polysorbate 20.

16. The composition of claim 1, further comprising a preservative.

17. The composition of claim 16, wherein the preservative is sodium benzoate.

18. The composition of claim 1, wherein the oral care composition is a mouthwash, a toothpaste, an oral gel or a dental powder.

19. An oral care composition consisting essentially of: water, an *Aloe vera* extract, zinc gluconate, zinc citrate, hydrogen peroxide, a *Matricaria chamomilla* (chamomile) extract, a cranberry extract, at least one surfactant, at least one flavoring agent, and at least one sweetener.

20. The composition of claim 19, wherein the surfactant is polysorbate 20.

21. The composition of claim 19, wherein the flavoring agent is *Mentha piperita* oil (peppermint oil), *Cinnamomum cassia* oil (cinnamon oil), or a combination thereof.

22. The composition of claim 19, wherein the sweetener is a stevia extract.

23. The composition of claim 19, further comprising a preservative.

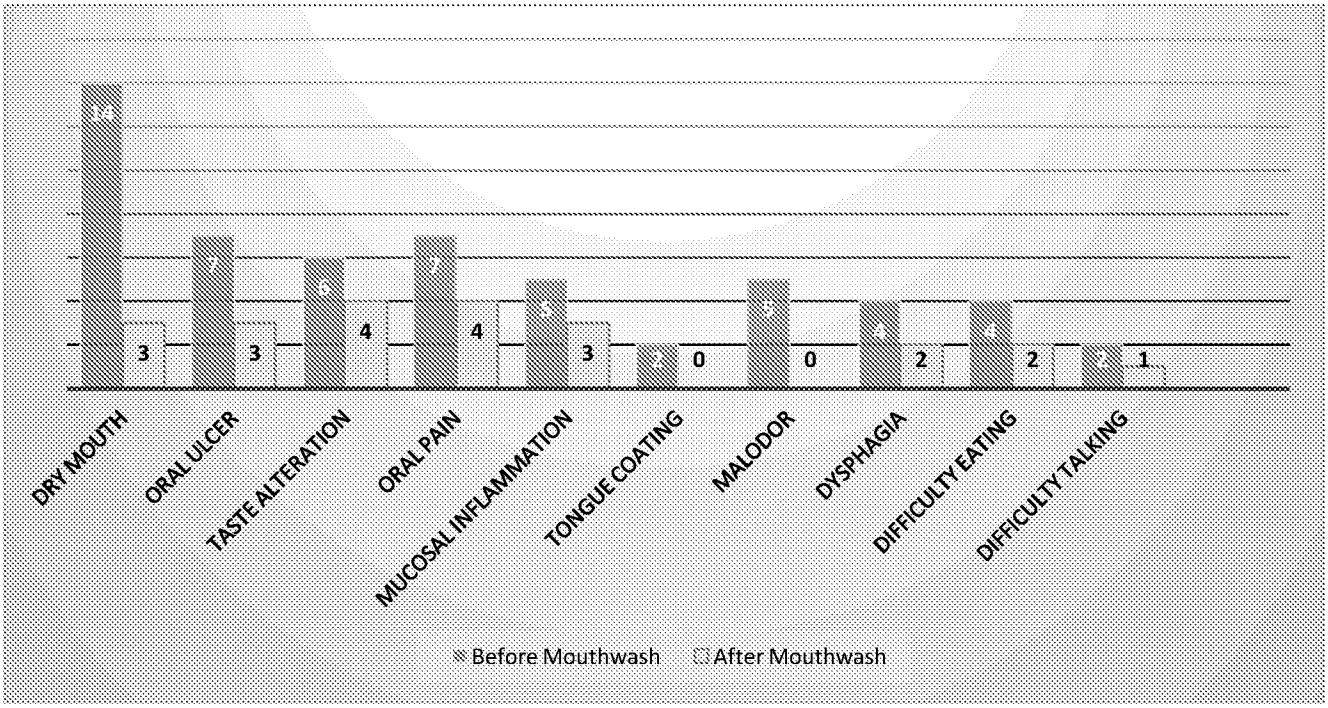
24. The composition of claim 23, wherein the preservative is sodium benzoate.

25. The composition of claim 19, wherein the weight percentages are:
about 80 – about 98% water, about 0.2 – about 5 wt% *Aloe vera* leaf extract (200:1 solution), about 0.2 – about 5 wt% zinc gluconate (dihydrate), about 0.01 – about 1 wt% zinc citrate, about 0.5 – about 5 wt% of 50% hydrogen peroxide, about 0.1 – about 2 wt% *Matricaria chamomilla* (chamomile) extract (1% solution), about 0.001 – about 0.5 wt% cranberry fruit extract, about 0.01 – about 0.5 wt% surfactant(s), about 0.001 – about 0.5 wt% flavoring agent(s), and about 0.01 – about 0.8 wt% sweetener(s); wherein the weight percentages are based on the total oral care composition.

26. An oral care composition consisting essentially of: about 90 – 95 wt% water, about 1 wt% *Aloe vera* leaf extract (200:1 solution), about 1 wt% zinc gluconate (dihydrate), about 0.2 wt% zinc citrate, about 2 wt% of 50% hydrogen peroxide, about 0.5 wt% of *Matricaria chamomilla* (chamomile) extract (1% solution), about 0.01 wt% cranberry fruit extract, about 0.1 wt% polysorbate 20, about 0.01 wt% *Cinnamomum cassia* oil (cinnamon oil), about 0.01 wt% *Mentha piperita* oil (peppermint oil), about 0.1 wt% stevia extract, and about 0.6 wt% sodium benzoate, wherein the weight percentages are based on the total oral care composition.

27. A method of improving or maintaining oral hygiene, or treating or preventing oral ulcers, oral infection or oral inflammation, the method comprising the step of applying the oral care composition of claims 1, 19, or 26.

Figure 1


14
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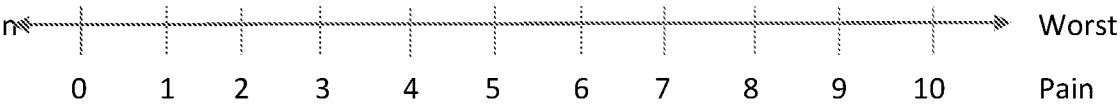
2
1
DRY MOUTH
ORAL ULCER
TASTE ALTERATION
ORAL PAIN
MUCOSAL INFLAMMATION
TONGUE COATING
MALODOR
DYSPHAGIA
DIFFICULTY EATING
DIFFICULTY TALKING
Before Mouthwash
After Mouthwash

Figure 2

PATIENT QUESTIONNAIRE

Date: _____ Time: _____ ☐ AM ☐ PM

Rate pain level of **oral or throat** discomfort:



Please answer ALL questions:

Able to eat?	☐ Yes	☐ No	If No, ☐ Little ☐ Nothing
Able to drink?	☐ Yes	☐ No	If No, ☐ Little ☐ Nothing
Difficulty swallowing?	☐ No	☐ Yes	If Yes, ☐ Foods ☐ Liquids
Mouth burning?	☐ No	☐ Yes	If Yes, ☐ With Foods ☐ With Liquids ☐ All the time
Difficulty eating?	☐ No	☐ Yes	If Yes, ☐ Foods that need to be chewed (i.e. meat, vegetables, fruits) ☐ Foods that do **NOT** need to be chewed (i.e. pudding, soup, supplemental drinks, yogurt)
Difficulty chewing?	☐ No	☐ Yes	
Mouth/Throat soreness?	☐ No	☐ Yes	
Dry mouth?	☐ No	☐ Yes	
Difficulty talking?	☐ No	☐ Yes	
Did you take medication for pain?	☐ No	☐ Yes	If Yes, please list medication, dose, and quantity

Please recall meals and drinks for the last 4 hours (include fast food meals, snacks, and supplemental drinks):

TIME	MEAL	DRINK

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/67367

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61Q 11/00; A61K 36/45, 9/08 (2016.01)
CPC - A61Q 11/00; A61K 36/45, 9/006
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)
IPC (8): A61K 9/08, 31/191, 31/315, 31/327, 31/716, 36/28, 36/45, 36/886; A61Q 11/00 (2016.01)
CPC: A61K 9/006, 9/08, 31/191, 31/315, 31/327, 31/716, 36/28, 36/45, 36/886, 45/05; A61Q 11/00; USPC: 424/724, 732, 764

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, RU, AT, CH, TH, BR, PH, INPADOC Data); Google Scholar; Google; , ProQuest; oral, dental, mouthwash, toothpaste, gel, powder, aloe vera, leaf, extract, gluconate, citrate, hydrogen peroxide, H2O2, dioxidane, oxidanyl, matricaria chamomilla, matricaria recutita, chamomile, cranberry, fruit, vaccinium macrocarpon, preventing, ulcer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2008/0118446 A1 (JABLOW, J) 22 May 2008; abstract; paragraphs [0002], [0005]-[0008], [0011], [0017], [0020]-[0026]	1-24, 27/1, 27/19
Y	US 2013/0330283 A1 (VOGT, R et al.) 12 December 2013; abstract; paragraphs [0011]-[0012], [0015]-[0016], [0022]-[0023], [0026], [0033]-[0034]	1-24, 27/1, 27/19
Y	US 2010/0152296 A1 (MARMARINOS, V et al.) 17 June 2010; abstract; paragraphs [0030]-[0031], [0039]	1-24, 27/1, 27/19
Y	WO 2009/146124 A1 (THE NATURAL DENTIST) 03 December 2009; page 5, first paragraph; page 11, third-fourth paragraphs; page 20, fourth, seventh paragraphs; page 21, second paragraph	5
Y	US 2003/0108627 A1 (SELZER, J et al.) 12 June 2003; paragraphs [0009]-[0011], [0019]	12, 22
Y	WO 2014/092733 A1 (COLGATE-PALMOLIVE COMPANY) 19 June 2014; paragraphs [0006]-[0007]	14-15, 20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"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
15 February 2016 (15.02.2016)	03 MAR 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)