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CA 2379703 A1 2001/02/08

(21) 2 379 703

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2000/07/28
(87) Date publication PCT/PCT Publication Date: 2001/02/08
(85) Entrée phase nationale/National Entry: 2002/01/11
(86) N° demande PCT/PCT Application No.: US 2000/020658
(87) N° publication PCT/PCT Publication No.: 2001/008671
(30) Priorité/Priority: 1999/07/30 (09/364,944) US

(51) Cl.Int.^{7}/Int.Cl.^{7} A61K 31/05, A61P 11/00

(71) Demandeur/Applicant:
THE PROCTER & GAMBLE COMPANY, US

(72) Inventeurs/Inventors:
GANTENBERG, NICHOLAS SEYMOUR, US;
SINGER, ROBERT ERNEST JR., US

(74) Agent: LEDGLEY, CYNTHIA J.

(54) Titre : PROCEDE ET COMPOSITION POUR LA PROPHYLAXIE ET LE TRAITEMENT DES SYMPTOMES LIES AUX AFFECTIONS DE TYPE RHUME ET D'ALLURE GRIPPALE

(54) Title: METHOD AND COMPOSITION FOR PROPHYLAXIS AND TREATMENT OF SYMPTOMS ASSOCIATED WITH COLD AND INFLUENZA-LIKE ILLNESSES

(57) Abrégé/Abstract:
The present invention relates to methods for the prophylaxis and treatment of symptoms associated with cold and influenza-like illnesses and/or the prophylaxis and treatment of congestion associated with respiratory afflictions, by administering a composition including a stilbenic phytoalexin preferably resveratrol. The invention further relates to certain stilbenic phytoalexin containing compositions useful for such methods.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/08671 A2

(51) International Patent Classification[7]: A61K 31/00

(21) International Application Number: PCT/US00/20658

(22) International Filing Date: 28 July 2000 (28.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/364,944 30 July 1999 (30.07.1999) US

(71) Applicant: **THE PROCTER & GAMBLE COMPANY** [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).

(72) Inventors: **GANTENBERG, Nicholas, Seymour**; 7097 Maple Creek Drive, Liberty Township, OH 45044-9211 (US). **SINGER, Robert, Ernest, Jr.**; 3 Kingsmont Court, Fairfield, OH 45014 (US).

(74) Agents: **REED, T., David** et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/08671 A2

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(57) Abstract: The present invention relates to methods for the prophylaxis and treatment of symptoms associated with cold and influenza-like illnesses and/or the prophylaxis and treatment of congestion associated with respiratory afflictions, by administering a composition including a stilbenic phytoalexin. The invention further relates to certain stilbenic phytoalexin containing compositions useful for such methods.

METHOD AND COMPOSITION FOR PROPHYLAXIS AND TREATMENT OF SYMPTOMS ASSOCIATED WITH COLD AND INFLUENZA-LIKE ILLNESSES

FIELD

The present invention relates to a novel therapeutic use of stilbenic phytoalexins. More specifically, the embodiments of the present invention relate to the prophylaxis and treatment of symptoms associated with cold and influenza-like illnesses and the prophylaxis and treatment of congestion associated with respiratory afflictions.

BACKGROUND

It is known that many different viruses and viral strains induce symptoms associated with respiratory viral infections. For example, the common cold and flu are caused by members of several families of viruses including influenza, parainfluenza viruses, rhinoviruses, respiratory syncytial viruses, enteroviruses, and coronaviruses. Pinpointing the specific cause of the illness is difficult and not practical since there are also a number of predisposing factors whose contribution to the manifestation of symptoms is not fully understood. Such factors include, but are not limited to, physical fatigue, psychological stress, and overall physical healthiness.

Regardless of the virus and associated factors leading to the onset of cold and influenza symptoms, a number of remedies to alleviate the symptoms of the common cold have been suggested. The cough/cold products that are currently marketed typically contain one or more of the following actives: nasal decongestants such as pseudoephedrine, oxymetazoline, antihistamines such as doxylamine, antitussives such as dextromethorphan, expectorants such as guaifenesin and antipyretics such as acetaminophen. In an attempt to improve existing cold remedies, experts in the field have suggested several alternative pharmacotherapies and subsequently conducted cold trials to test their efficacy.

Examples of these therapies include the use of interferon-α_2 , see Douglas et al., Prophylactic Efficacy of Intranasal Alpha$_2$- Interferon Against Rhinovirus Infection in the Family Setting, The New England Journal of Medicine, 314, pp. 65-70, 1986; bradykinin antagonist, see Higgins et al., A Study of the Efficacy of the Brandykinin Antagonist, NPC567, in Rhinovirus Infections in Human Volunteers, Antiviral Research vol. 14, pp. 339-344, 1990; glucocorticoid, see Farr et al., A Randomized Controlled Trial of Glucocorticoid Prophylaxis Against Experimental Rhinovirus Infection, The Journal of Infectious Diseases vol. 162, pp. 1173-1177, 1990; nedocromil, see Barrow et al., The Effect of Intranasal Nedocromil Sodium on Viral Upper Respiratory Tract Infections in Human Volunteers, Clinical and Experimental Allergy vol. 20, pp. 45-51, 1990; a combination of interferon-α_2, ipratropium and naproxen, see Gwaltney; Combined Antiviral and Antimediator Treatment of Rhinovirus Colds, The Journal of Infectious Diseases vol. 166, pp. 776-782, 1992; and zinc salts, see Potter et al., DIAS Rounds, Zinc Lozenges for Treatment of Common Colds, The Annals of Pharmacotherapy vol. 27, pp. 589-592, 1993.

A number of patents have also been issued disclosing compositions for the treatment of the common cold and flu symptoms and their methods of use. A sample of such patents include: U.S. Patents 5,240,694; 5,422,097, and 5,492,689, all to Gwaltney, disclosing treatment using combinations of antiviral and antiinflammatory compounds; U.S. Patents RE033,465 and 5,409,905, both to Eby disclosing treatment using zinc salts; and U.S. Patents 4,619,934 and 4,552,899, both to Sunshine, disclosing treatment of cough and colds using compositions comprising non-steroidal antiinflammatory drugs such as NSAIDS with antihistaminically effective materials such as chlorpheniramine. Despite the abundance of compositions and preventative treatments known in the art, there remains a need to provide a consistent, effective, and safe method for the prophylaxis and treatment of cold and influenza-like symptoms as well as treatment of congestion associated with respiratory afflictions.

As discussed in detail below, Applicants have discovered new means for the prophylaxis and treatment of cold and influenza-like symptoms as well as

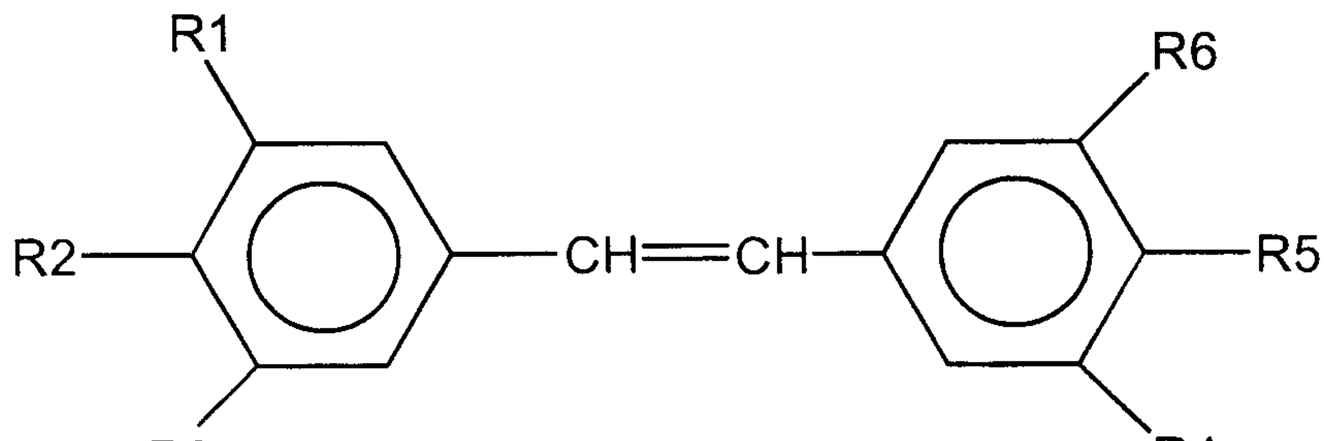
treatment of congestion associated with respiratory afflictions via administration of certain stilbenic phytoalexins.

Phytoalexins are defense substances with antimicrobial properties which are produced by plants after infections. They include various groups of natural substances (e.g., isoflavonoids, terpenoids, polyacetylenes and dihydrophenanthrenes). Different sources of phytoalexin include the roots of *Veratrum grandiflorum*, the bark of *Pinus sibirica*, *Vitis vinifera*, and *Arachis hypogaea*. Other sources include *Eucalyptus*, *Polygonum* and *Nothofagus* species and *Cudrania javanensis*. Phytoalexins can also exist naturally as an oligomer.

Compositions comprising stilbenic phytoalexins can be prepared either utilizing natural occurring sources of stilbenic phytoalexins or synthesizing stilbenic phytoalexins. One type of stilbenic phytoalexin that can be found in a variety of naturally occurring sources is 3,4',5-trihydroxystilbene resveratrol. Reservatrols are found in relatively large amounts in red grapes and red wine and implicated for favorable pharmacological effects that include the prevention and therapy of atherosclerosis. Research conducted on the components present in red wine that exert pharmacological effects indicates 3,4',5-trihydroxystilbene resveratrol's protective effects at the cardiovascular level. See, for example, Frankel E. N., et al., 341 Lancet 454, 1993. Recently, it has been demonstrated that 3,4',5-trihydroxystilbene resveratrol has activity as a cancer chemopreventive (Meishang Jang et al., 275 Science 218-229, 1997). The dietary supplement Huzhang, a source of resveratrol, is reported to have antioxidant properties (product label for Resveratrol from "Source Naturals," 1997).

SUMMARY

The present invention is directed to methods for the prophylaxis and treatment of cold and influenza-like symptoms and/or treatment of congestion associated with respiratory afflictions comprising administering to a subject a composition having a stilbenic phytoalexin having the structure:



wherein R^1, R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen and hydroxy.

The present invention is further directed to compositions including the above stilbenic phytoalexin.

DETAILED DESCRIPTION

While the specification concludes with claims which particularly point out and distinctly claim the invention, it is believed the present invention will be better understood from the following description.

All cited references are incorporated herein by reference in their entireties. Citation of any reference is not an admission regarding any determination as to its availability as prior art to the claimed invention.

All percentages are by weight of total composition unless specifically stated otherwise.

All ratios are weight ratios unless specifically stated otherwise.

Herein, "comprising" means that other steps and other ingredients which do not affect the end result can be added. This term encompasses the terms "consisting of" and "consisting essentially of".

Herein, "safe and effective amount" means an amount of active high enough to provide a significant positive modification of the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment. A safe and effective amount of active will vary with the particular condition being treated, the age and physical condition of the subject being treated, the severity of the condition the duration of the treatment, the nature of concurrent therapy and like factors.

Non-limiting symptoms associated with cold and influenza-like illnesses include nasal congestion, sneezing, sinus pain, sore throat, runny nose, cough, chest pain and headaches. In addition, congestion is associated with certain

respiratory afflictions. These respiratory afflictions include viral, bacterial, and fungal infections which may lead to sinusitis, otitis media, and pneumonia. Other respiratory afflictions that result in congestion include inflammatory and immunological responses to allergens and pollutants.

Nasal congestion is one manifestation of congestion generally. Congestion is characterized by localized edema at tissues or organs that are inflamed or injured in response to colds and respiratory ailments. To this end, congestion is accompanied by increased fluid production at mucus producing tissues such as the nose, lungs, and throat. The increased fluid production is responsible for reducing airflow through a lumenal site such as nasal passages or even the lungs. Other locations that become congested include the head or facial sinuses, ear canals, and the throat. Sinus and otic openings (ostia) are usually kept open by normal cellular processing of mucus, foreign particles and bacterial imbalances. However, these locations and openings can become clogged due to excessive edema which results in sinus, middle ear or head pain. The pain is believed to result from the increased pressure in the sinuses following a fluid influx that is coincident with an inflammatory cell influx which results, in part, to make more mucus or frank pus. Therefore, it is generally accepted that nasal congestion is associated and may be coincident with these conditions. Nasal congestion results in the sensation of one's nose and nasal passages being blocked with the inability to conduct airflow through the nares.

One method of measuring such blockage is by measuring a subject's nasal airway resistance (NAR). NAR is a physical measure of resistance to air flow, calculated from pressure gradients, through the nasal passage (e.g. nares, turbinates) under normal breathing patterns. Congestion in nasal tissues increases NAR. Increases in NAR coincide with the sensation of blocked and/or clogged airways. The biological mechanisms in nasal congestion are relevant to both symptoms associated with cold and influenza-like illnesses and congestion associated with respiratory afflictions.

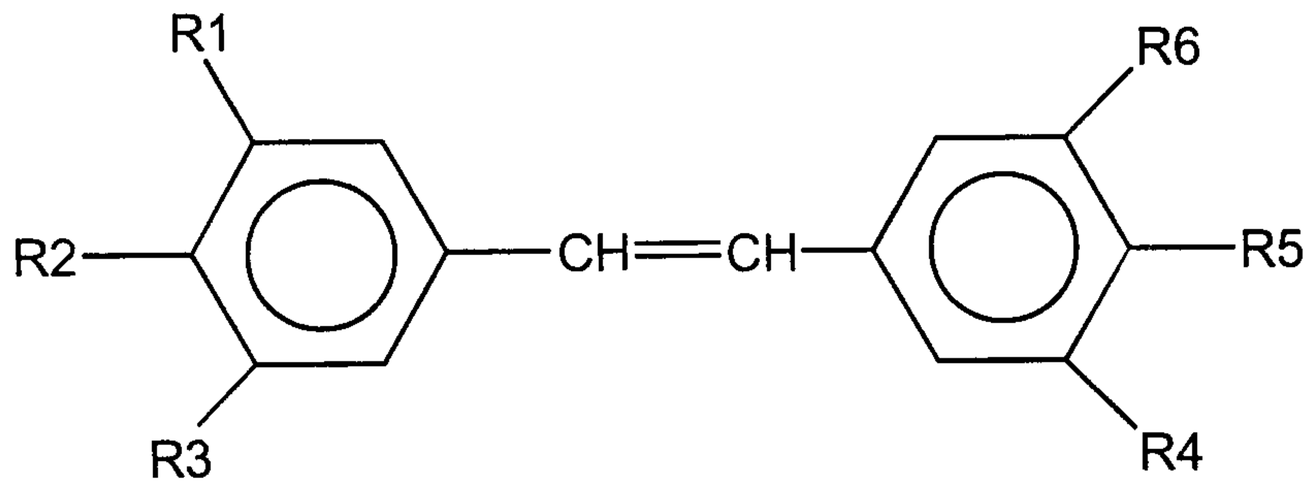
NAR is measured by acoustic and passive rhinometry. Amis, T.C., Oral airway flow dynamics in healthy humans, 515 J. Physiol. Lond. 293-8, 1999; Baroody, F.M. Relationship between histamine and physiological changes during

the early response to nasal antigen provocation, 86 J. Appl. Physiol. 659-68, 1999; Hilberg, O., Acoustic reflections during rhinometry: spatial resolution and sound loss, 84(3) J. Appl. Physiol. 1030-9, 1998; Hilber, O., Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection, 66(1) J. Appl. Physiol., 295-303, 1989 are cited as references incorporated herein.

A. Method

Applicants have surprisingly discovered stilbenic phytoalexins of Formula 1 are useful in the prophylaxis and treatment of symptoms associated with cold and influenza like illnesses as well as congestion associated with respiratory afflictions. For example, administering a safe and effective amount of a stilbenic phytoalexin of the present invention to a subject already suffering from nasal congestion decreases NAR by; preferably about 70% to about 98%; more preferably about 80% to about 95%; even more preferably about 85% to about 94%. In another example, administering a safe and effective amount of a stilbenic phytoalexin of the present invention to a subject prior to suffering from nasal congestion minimizes increases in NAR by; preferably about 70% to about 98%; more preferably about 80% to about 95%; even more preferably about 85% to about 94%.

An embodiment of the present invention relates to a method for the prophylaxis and treatment of cold and influenza-like symptoms including administering to a subject a composition including a stilbenic phytoalexin having the following chemical Formula 1:



Formula 1

where R^1, R^2, R^3, R^4, R^5, and R^6 are independently hydrogen or hydroxyl; and medicinally acceptable salts or esters thereof.

Preferably "R" represents mixtures of hydrogen and hydroxyl More preferably the stilbenic phytoalexin is a tetrahydroxystilbene or trihydroxystilbene; more preferably still, 3,4',5 - trihydroxystilbene resveratrol (hereinafter "resveratrol"), i.e., where R^1, R^3, R^5, and are hydroxyl and R^2, R^4, and R^6 are hydrogen.

Such compositions useful in the methods of the present invention are discussed in more detail, below.

B. Compositions

An embodiment of the present invention relates to compositions having a stilbenic phytoalexin of Formula 1.

Preferably the compositions useful in the present invention include from about 0.01% to about 99.99% of the stilbenic phytoalexin of Formula 1; more preferably from about 0.05% to about 30%; and more preferably still from about 0.1% to about 25%.

1. Pharmaceutical Agents

A preferred embodiment of the present invention relates to compositions including a stilbenic phytoalexin of Formula 1, above, in combination with a pharmaceutical agent. A non-limiting list of pharmaceutical agents useful in the present invention, with examples, include:

Antihistamines, including, Hydroxyzine, Pyrilamine, Phenindamine, Dexchlorpheniramine, Clemastine Diphenhydramine, Azelastine, Acrivastine, Levocarbastine, Mequitazine, Astemizole, Ebastine, Loratadine, Cetirizine, Terfenadine, Promethazine, Dimenhydrinate, Meclizine, Tripelennamine, Carbinoxamine, Cyproheptadine, Azatadine, Brompheniramine, Triprolidine, Cyclizine, Thonzylamine, Pheniramine, and mixtures thereof.

Antitussives, including, Hydrocodone, Noscapine, Benzonatate, Diphenhydramine, Chlophedianol, Clobutinol, Fominoben, Glaucine, Pholcodine, Zipeprol, Hydromorphone, Carbetapentane, Caramiphen, Levopropoxyphene, Codeine, Dextromethorphan, and mixtures thereof.

Antiinflammatories, preferably Non-Steroidal Anti-inflammatories (NSAIDS) including, Ketoprofen, Indoprofen, Indomethacin, Sulindac, Diflunisal, Ketorolac, Piroxicam, Meclofenamate, Benzydamine, Carprofen, Diclofenac,

Etodolac, Fenbufen, Fenoprofen, Flurbiprofen, Mefenamic, Nabumetone, Phenylbutazone, Pirprofen, Tolmetin, Ibuprofen, Naproxen, Sodium naproxen, Aspirin, and mixtures thereof.

Analgesics, including, Acetaminophen.

Expectorants/Mucolytics, including, Ambroxol, Bromhexine, Terpin, Guaifenesin, Potassium iodide, N-Acetylcysteine, and mixtures thereof.

Mast Cell Stabilizers, preferably intranasally, or orally administered mast cell stabilizers, including, Cromolyn, Oxatamide, Ketotifen, Lodoxamide, Nedocromil, and mixtures thereof.

Leukotriene Antagonists, including, Zileuton and others.

Methylxanthines, including, Caffeine, Theophylline, Enprofylline, Pentoxifylline, Aminophylline, Dyphylline, and mixtures thereof.

Antioxidants or radical inhibitors, including, Ascorbic acid, Tocopherol, Pycnogenol, and mixtures thereof.

Steroids, preferably intranasally administered steroids, including, Beclomethasone, Fluticasone, Budesonide, Mometasone, Triamcinolone, Dexamethasone, Flunisolide, Prednisone, Hydrocortisone and mixtures thereof.

Bronchodilators, preferably for inhalation, including, Albuterol, Epinephrine, Ephedrine, Metaproterenol, Terbutaline, Isoetharine, Terbutaline, Isoetharine, Pirbuterol, Bitolterol, Fenoterol, Rimeterol, Ipratroprium, and mixtures thereof.

Antivirals, including, Amantadine, Rimantadine, Enviroxime, Nonoxinols, Acyclovir, Alpha-Interferon, Beta-Interferon, and mixtures thereof.

Biologics, including, cytokine and celladhesion molecule inhibitors, ICAM antagonists, interleukin agonists or antagonists, hormones, polypeptides, amino acids, nucleotides, antibodies, and mixtures thereof.

The acid or base addition salts, esters, metabolites, stereoisomers and enantiomers of these actives are also contemplated as pharmaceutical agents useful in certain embodiments of the present invention, as well as the analogues of these actives that are safe and effective. It is also recognized that a pharmaceutical agent may be useful for more than one of the above uses, and these uses are clearly contemplated as well. This overlap is recognized in the art

and adjusting dosages and the like to fit the indication is well within the purview of the skilled medical practitioner.

2. Enhancing Agents

In a preferred embodiment, the composition further includes an enhancing agent. Enhancing agents useful in the present invention include, but not limited to, herbs, phenols, polyphenols, anthocyamins, anthocyanosides, carotenoids, bioflavinoids, vitamins, metal ions, mineral salts, proanthocyanidins, antioxidants, and/or vegetal fibers. Non-limiting examples include echinacea, tea polyphenols, epigallocatechin, beta carotene, grape seed extracts, lycopenes, flavones, quercetin, tocopherol, zinc, selenium, stannous, ascorbic acid, calcium, N-acetyl cysteine, and mixtures thereof.

3. Sources of Stilbenic Phytoalexins

The stilbenic phytoalexin of Formula 1 may originate from natural and/or synthetic sources. Orsini-F, et al., Isolation, synthesis, and antiplatelet aggregation activity of resveratrol 3-O-beta-D-glucopyranoside and related compounds, 60(11) J. Nat. Prod. 1082-7, 1997: Orsini-F, et. al., Synthesis of biologically active polyphenolic glycosides (combretastatin and resveratrol series), 301(3-4) Carbohydr. Res. 95-109, 1997: Hain, et. al., Expression of a stilbene synthase gene in Nicotiana tabacum results in synthesis of the phytoalexin resveratrol, 15(2) Plant. Mol. Biol. 325-35, 1990 are cited as references incorporated herein.

In a preferred embodiment, the composition includes natural source products, natural source extracts, or natural source powders of the stilbenic phytoalexins of Formula 1. Non-limiting examples include wine, grapes, Huzhang, and *Polygonum cuspidatum*.

4. Form and Administration

The compositions useful in the present invention may be a solid, semi-solid, liquid, semi-liquid; in the form of powders, granules, liposomes, tablets, capsules, gels, lozenges, dentifrice, and mouthwash.

The compositions useful in the present invention may be incorporated into microspheres, microcapsules, nanoparticles, liposomes and the like for controlled release. Furthermore, the compositions may, in addition, conveniently comprise

suspending, solubilizing, stabilizing, pH-adjusting agents and/or dispersing agents.

In a preferred embodiment, the composition is in the form of a herbal medicament. Herbal medicament forms useful in the present invention include, but are not limited to, teas, decoctions, beverages, candies or other confection, foods, enteral liquid nutritional products, mouthwashes, lozenges, dentifrices, and dietary or nutritional supplements.

The administrative route of the compositions of the present invention includes any suitable route which leads to a concentration in the blood that provides a prophylactic and treatment benefit. Suitable administration routes include, but are not necessarily limited to: oral, oral topical, parenteral, cutaneous, nasal, rectal, vaginal, ocular, inhalant, or combinations thereof. Preferably the administrative route is oral or nasal.

EXAMPLES

The following examples further describe and demonstrate the preferred embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration, and are not to be construed as limitations of the present invention since many variations thereof are possible without departing from its spirit and scope. All ingredients are by weight of 100 grams of the composition:

Examples 1 and 2

Examples of toothpaste and tooth gel compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 1 (Wt. %)	Example 2 (Wt. %)
Sorbitol	41.44	35.00
Saccharin Sodium	0.46	0.20
FD&C Blue (1% sol'n)	-------	0.05
Precipitated Silica	20.00	25.00
Sodium Fluoride	0.24	0.24
Flavor	1.00	1.50
Sodium Alkyl Sulfate	4.00	1.20
Trisodium Phosphate	1.45	------

Monosodium Phosphate	0.59	------
Carbopol 940	0.30	0.25
Xanthan Gum	0.48	0.65
Titanium Dioxide	0.53	------
Resveratrol	2.00	1.00
Purified Water	q.s.	q.s.

Examples 3 and 4

Examples of mouthwash compositions of the subject invention are made by conventional processes by mixing the following:

Ingredients	Example 3 (Wt. %)	Example 4 (Wt. %)
Cetylpyridinium Chloride	0.045	0.045
Domiphen Bromide	0.005	0.005
Alcohol (Standard Denatured No. 40)	16.25	8.50
Glycerin	10.00	7.50
Poloxamer 407	0.20	0.20
Sodium Hydroxide	0.003	0.003
Sodium Benzoate	0.05	0.54
Benzoic Acid	0.005	0.003
Tween 80	0.03	0.12
FD&C Green (1% sol'n)	0.04	0.12
FD&C Blue (1% sol'n)	0.003	------
FD&C Yellow (1% sol'n)	-------	0.001
Saccharin	0.06	0.08
Peppermint Oil	0.14	-------
Spearmint Oil	-------	0.12
Resveratrol	0.30	0.20
Purified water	q.s.	q.s.

Example 5

An example of a dental solution of the subject invention is made by mixing the following:

Ingredients	(Wt. %)
Resveratrol	1.00
Flavor	0.10
Polysorbate 80	0.25
Saccharin Sodium	0.05
Methylparaben	0.20
Propylparaben	0.10
Water	q.s.

Example 6

An example of an oral gel composition of the subject invention is made by mixing the following:

Ingredients	(Wt. %)
Hydroxyethyl Cellulose	2.50
Sodium Fluoride	0.09
Saccharin Sodium	0.05
FD&C Green No. 3 (1% sol'n)	0.01
Resveratrol	1.00
Purified Water	q.s.

Example 7

An example of an intranasal spray solution is made by mixing the following:

Ingredient	Grams
Resveratrol	1.0
Nonionic detergent [1]	0.70
Dibasic sodium phosphate	0.11
Monobasic potassium phosphate	0.38
Benzalkonium chloride	0.04
Chlorhexidine gluconate	0.26
Disodium EDTA	0.01
Flavoring [2]	
Camphor and eucalyptol [3]	
Purified water QS to 100 grams	

1 Available as Tyloxapol from Nycomed, Inc.

2 Flavoring used at a level in order to provide a pleasing taste.

3 Added at a level in order to provide a pleasant in-use scent.

Add all ingredients to chilled water and stir until dissolved , while maintaining the chilled water temperature. Adjust this solution to pH of 5.5 to 6.5. QS with water and filter through a cellulose acetate membrane filter. Fill manually operated nasal sprayers with the composition. Spray from about 5 to 500 microliters of solution into each nostril. Repeat three times daily.

Example 8

An example of an intranasal drop solution is made by mixing the following:

Ingredients	Grams
Methylcellulose gum	0.115
Sodium chloride	0.350
Monobasic potassium phosphate	0.540
Dibasic potassium phosphate	0.310
Poloxamer block co-polymer [1]	0.145
Propylene glycol	1.170
Resveratrol	0.568
Benzalkonium chloride	0.025
Flavoring [2]	
Camphor and eucalyptol [3]	
Purified water QS to 100 grams	

1 Available as Pluronic 127 from BASF Corporation.

2 Flavoring used at a level in order to provide a pleasing taste.

3 Added at a level in order to provide a pleasant in-use scent.

Add all ingredients except methylcellulose to chilled water and stir until dissolved, while maintaining the chill water temperature. Adjust this solution to pH of 6.5 - 7.0 and filter through a cellulose acetate membrane filter. Add the methylcellulose to the chilled solution, QS with water, and stir under refrigeration to hydrate. Fill dropper vials with the solution and cap. Apply one drop of the solution to each nostril with the head tilted upward. Hold head briefly in this

position to permit spreading of the solution over the nasal turbinates. Repeat 3 times daily.

Example 9

An example of an intranasal powder is made by mixing the following:

Ingredients	Grams
Resveratrol	5.0
Dextrose powder	1.0
Ethanol	1.0
Flavoring [1]	
camphor and eucalyptol [2]	
Lactose powder QS to 100 grams.	

1 flavoring is used in an appropriate amount to provide a pleasing taste.

2 added at an appropriate level to provide a pleasant in use scent.

Mix resveratrol with the dextrates in a V-mixer. Micronize this mixture in a fluid energy mill at 100 pounds per square inch dry air pressure. Mix the micronized material by geometric addition with the lactose in a V-mixer. Dissolve camphor, eucalyptol, and flavors in ethanol, spray coating the powder with the liquid in a V-mixer. Evaporate the ethanol after mixing by pan drying. Fill dry powder nasal inhalation metering pumps with the powder. Such pumps include Prohaler DPI from Valois Corporation. Apply ten milligrams of the powder to each nostril while inhaling. Repeat three times daily.

Example 10

An example of an inhalant is made by mixing the following:

Ingredients	Grams
Resveratrol	0.60
Sorbitan trioleate	0.40
Propellant 114[1]	49.50
Propellant[2]	49.51

1 Freeon 114 E.I. Dupont

2 Freeon 12 E.I. Dupont

Micronize the resveratrol in a fluid energy mill at 100 pounds per square inch pressure. Dissolve the sorbitan trioleate in the mixed propellants. Disperse the resveratrol in the sorbitan trioleate / propellant liquid. Fill the suspension in to the canister of a pressurized metered dose inhaler using standard filling techniques. Administer 100 to 200 microliters from the metered dose inhaler into the mouth, while inhaling.

Example 11

An example of sublingual tablet made by mixing the following:

Ingredients	Grams
Resveratrol	10
Lactose	86
Sucrose	87
Acacia	10
Talc	6
Magnesium stearate	1
Water	q.s.

Put resveratrol and excipient through a 60-mesh screen and blend. Moisten with water to make a stiff mass; pass through an 8-mesh screen and dry at 40C. Reduce the particle size by passing the dried granulation through a 10-mesh screen; blend in lubricants and compress. Mold tablet into a flat, elliptical or capsule-shaped tablet. Place tablet under tongue or between gum and cheek.

Example 12

An example of sublingual tablet made by mixing the following:

Ingredients	Grams
Resveratrol	4.4
Lactose	32.25
Polyethylene glycol	0.35
Alcohol-water (60:40)	q.s.

Screen and blend powders; moisten the blend with alcohol-water (60:40) to which the polyethylene glycol has been added, and mold the tablets into a flat, elliptical or capsule-shaped tablet. Place tablet under tongue or between gum and cheek.

Example 13

An example of a liquid composition administered to the sublingual mucosae or in the buccal cavity.

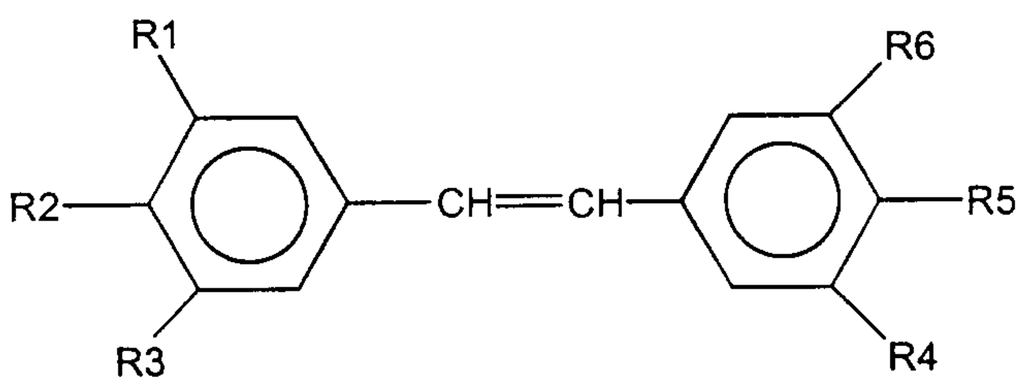
Ingredients	Grams
Resveratrol	5
Ethanol	80
Mineral oil	12
Hydroxypropyl cellulose	2
Menthol	1
Water	q.s.

Lastly, methods and compositions of the present invention are further believed to improve the general maintenance and wellness of respiratory health. Indeed the prophylactic effect of the stilbenic phytoalexins of Formula 1 on symptoms, are believed to be attributable, in part, to increased general respiratory health

While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can be practiced with considerable modification within the spirit and scope of the appended claims.

What is claimed is:

1. A process for making a composition for wherein said composition is used as a prophylaxis and treatment of cold and influenza-like symptoms and congestion associated with respiratory afflictions said compositions comprising a stilbenic phytoalexin having the structure:



wherein R^1, R^2, R^3, R^4, R^5, and R^6 are independently selected from hydrogen and hydroxy; and medicinally acceptable salts or esters thereof.

2. The process of Claim 1 wherein the stilbenic phytoalexin is a trihydroxystilbene or tetrahydroxystilbene, preferably 3,4',5-trihydroxystilbene resveratrol.

3. The process of Claims 1-2 wherein the composition comprises from 0.01% to 99.99% of the stilbenic phytoalexin.

4. The process of Claims 1-3 wherein the composition further comprises natural source products, natural source extracts, or natural source powders of the stilbenic phytoalexin.

5. The process of Claims 1-4 wherein the composition is a herbal medicament.

6. The process of Claims 1-5 wherein the composition is a solid, semi-solid, liquid, or semi-liquid, in the form of powders, granules, liposomes, tablets, capsules, gels, lozenges, dentifrices, and mouthwashes.

7. The process of Claims 1-6 wherein the composition further comprises an enhancing agent selected from the group consisting of herbs, phenols, polyphenols, anthocyamins, anthocyanosides, carotenoids, bioflavinoids, vitamins, mineral salts, metal ions, antioxidants, vegetal fibers, and mixtures thereof.

8. The process of Claims 1-7 wherein the composition comprises a pharmaceutical agent selected from the group consisting of antihistamine, antitussive, antiinflammatory, analgesic, mast cell stabilizer, leukotriene antagonist, methylxanthine, antioxidant, steroid, bronchodilator, antiviral, biologic, and mixtures thereof.