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SUPERINTENDENCIA V. REGISTRO

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Dependenc.a. 2283 DIVISION DE NUEVAS CREACIONES

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 00057176

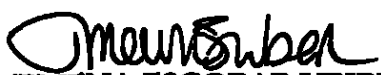
Solicitud de Patente en nombre de

THE PROCTER & GAMBLE COMPANY

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Santafé de Bogotá, en la Carrera 11 A No 94-76 Of. 305, obrando como apoderada de la sociedad THE PROCTER & GAMBLE COMPANY solicitante de la patente de la referencia, anexo al presente memorial el siguiente documento:

Copia certificada de la solicitud de Patente Número 09/364,944 presentada en los Estados Unidos de América el día 30 de julio de 1999, con la debida traducción de lo pertinente, incluyendo el capítulo reivindicatorio

Señor Superintendente,


JIMENA ESCOBAR URIBE

C.C.39.779.452 de usaquén

T.P. 68228

Cód. 5376

A2

**ESTADOS UNIDOS DE AMERICA
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**DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS
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Julio 13, 2000

La presente es para certificar que el anexo es una copia fiel de los registros de la Oficina de Patentes y Marcas de los Estados Unidos, de los documentos de la solicitud de patente identificada más adelante, que cumplieron con los requerimientos para concederse una fecha de presentación de acuerdo con 35 USC 111

Número de Solicitud 09/364,944

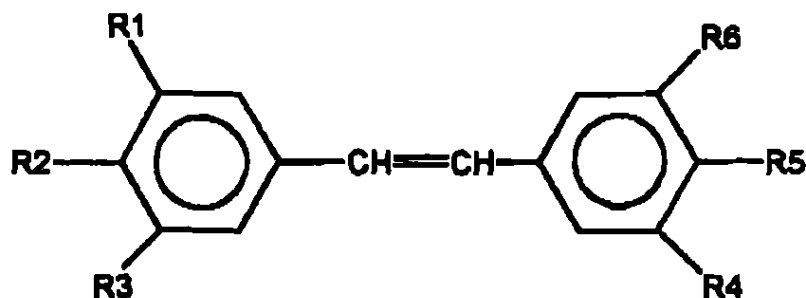
Fecha de Presentación Julio 30, 1999

**Por la autoridad del
Comisionado de Patentes y Marcas**

**(fdo) E EDELEN
Oficial Certificador
Sello oficial de la Oficina de Patentes y Marcas de los
Estados Unidos de América**

REIVINDICACIONES

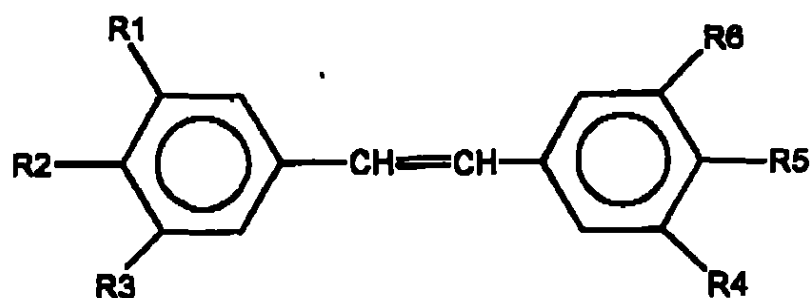
1. Un método para la profilaxis y tratamiento de síntomas del resfriado y similares a la influenza que comprende la administración a un sujeto de una composición que incluye una fitoalexina estilbénica que tiene la estructura.



en donde R^1 , R^2 , R^3 , R^4 , R^5 y R^6 Independientemente se seleccionan de hidrógeno e hidroxil, y sales o ésteres medicinalmente aceptables de estos.

- 2 El método de la Reivindicación 1 en donde la fitoalexina estilbénica es un trihidroxiestilbeno o tetrahidroxiestilbeno.
- 3 El método de la Reivindicación 2 en donde la fitoalexina estilbénica es 3,4',5-trihidroxiestilbeno resveratrol
- 4 El método de la Reivindicación 1 en donde la composición comprende de 0,01% a 99,99%, aproximadamente, de la fitoalexina estilbénica
- 5 El método de la Reivindicación 4 en donde la composición adicionalmente comprende productos de fuentes naturales, extractos de fuentes naturales, o polvos de fuentes naturales de la fitoalexina estilbénica.

6. El método de la Reivindicación 4 en donde la composición es una medicina herbal.
7. El método de la Reivindicación 4 en donde la composición es un sólido, semisólido, líquido, o semilíquido en la forma de polvos, gránulos, liposomas, tabletas, cápsulas, geles, pastillas, dentríficos, y enjuagues bucales.
8. El método de la Reivindicación 4 en donde la composición adicionalmente comprende un agente mejorador que se selecciona del grupo que consiste de yerbas, fenoles,, polifenoles, antoclaminas, antocianosidas, carotenoides, bioflavonoides, vitaminas, sales minerales, iones metálicos, antioxidantes, fibras vegetales, y mezclas de estos.
9. El método de la Reivindicación 4 en donde la composición comprende un agente farmacéutico que se selecciona del grupo que consiste de antihistamina, antitusivo, antiinflamatorio, analgésico, estabilizante de células mástiles, antagonista de leucotrieno, metilxantina, antioxidante, esteroide, broncodilatador, antiviral, biológico, y mezclas de estos
10. El método para la profilaxis y tratamiento de la congestión asociada con padecimientos respiratorios que comprende la administración a un sujeto de una composición que comprende una fitoalexina estilbénica que tiene la estructura:

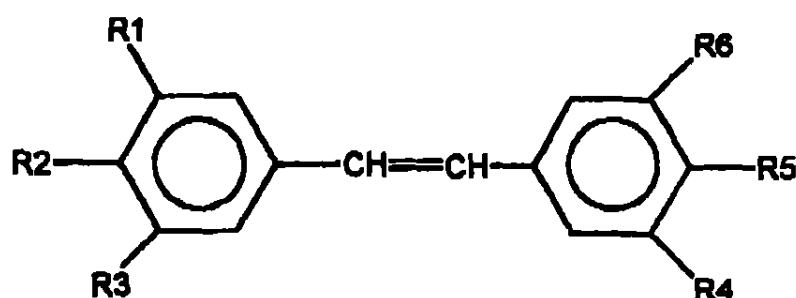


en donde R^1 , R^2 , R^3 , R^4 , R^5 , y R^6 independientemente se seleccionan de hidrógeno e hidroxil; y sales o ésteres medicinalmente aceptables de estos.

11. El método de la Reivindicación 10 en donde la fitoalexina estilbénica es un trihidroxiestilbeno o tetrahidroxiestilbeno.
12. El método de la Reivindicación 11 en donde la fitoalexina estilbénica es 3,4',5-trihidroxiestilbeno resveratrol
13. El método de la Reivindicación 10 en donde la composición comprende de 0,01% a 99,99%, aproximadamente, de la fitoalexina estilbénica
14. El método de la Reivindicación 13 en donde la composición adicionalmente comprende productos de fuentes naturales, extractos de fuentes naturales, o polvos de fuentes naturales de la fitoalexina estilbénica
15. El método de la Reivindicación 13 en donde la composición es una medicina herbal
16. El método de la Reivindicación 13 en donde la composición es un sólido, semisólido, líquido, o semilíquido en la forma de polvos, gránulos, liposomas, tabletas, cápsulas, geles, pastillas, dentríficos, y enjuagues bucales.

- 17 El método de la Reivindicación 13 en donde la composición adicionalmente comprende un agente mejorador que se selecciona del grupo que consiste de yerbas, fenoles,, polifenoles, antoclaminas, antocianosidas, carotenoides, bioflavinoideas, vitaminas, sales minerales, iones metálicos, antioxidantes, fibras vegetales, y mezclas de estos.
18. El método de la Reivindicación 13 en donde la composición comprende un agente farmacéutico que se selecciona del grupo que consiste de antihistamina, antitusivo, antiinflamatorio, analgésico, estabilizante de células mástiles, antagonista de leucotrieno, metilxantina, antioxidante, esteroide, broncodilatador, antiviral, biológico, y mezclas de estos.
- 19 Una composición que comprende

a) una fitoalexina estilbénica que tiene la estructura



en donde R^1 , R^2 , R^3 , R^4 , R^5 , y R^6 independientemente se seleccionan de hidrógeno e hidroxilo, y sales o ésteres médicamente aceptables de estos.

b) un agente farmacéutico que se selecciona del grupo que consiste de antihistamina, antitusivo, antiinflamatorio, analgésico, estabilizante de células mástiles, antagonista

de leucotrieno, metilxantina, antioxidante, esteroide, broncodilatador, antiviral, biológico, y mezclas de estos.

20. La composición de la Reivindicación 19 en donde la fitoalexina estilbénica es 3,4',5-trihidroxiestilbeno resveratrol.

PS 274348



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

July 13, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/364,944

FILING DATE: July 30, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

L. Edelen

**L. EDELEN
Certifying Officer**

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+

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PTO/SB/05 (12/97)

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**UTILITY
PATENT APPLICATION
TRANSMITTAL**

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No. 7000 Total Pages 25

First name Inventor or Application Identifier

Nicholas Seymour Gentenberg

Robert Ernest Singer, Jr

Express Mail Label No. EJ302200351US

APPLICATION ELEMENTS

See MPEP Chapter 600 concerning utility patent application contents.

ADDRESS TO:

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1 ☒ Fee Transmittal Form
(Submit an original, and a duplicate for fee processing)

2 ☒ Specification Total Pages 22

(preferred arrangement set forth below)

- Descriptive Title of the Invention

- Cross References to Related Applications

- Statement Regarding Fed sponsored R&D

- Reference to Microfiche Appendix

- Background of the Invention

- Brief summary of the Invention

- Brief Description of the Drawings (if filed)

- Detailed Description

- Claim(s)

- Abstract of the Disclosure

3 ☐ Drawing(s) (35 USC 113) Total Sheets ☐

4 Oath or Declaration

a ☒ Newly executed (original or copy)

b ☐ Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 17 completed)
(Note Box 5 below)

i ☐ **DELETION OF INVENTORS**

Signed statement attached deleting

Inventor(s)

named in the prior application, see 37 CFR
1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference (useable if Box 4b is checked)

6 ☐ Microfiche Computer Program (Appendix)

7 Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)

a ☐ Computer Readable copy

b. ☐ Paper Copy (identical to computer copy)

c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))

9 ☐ 37 CFR 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)

10 ☐ English Translation Document (if applicable)

11 ☐ Information Disclosure ☐ Copies of IDS
Statement (IDS)/PTO-1449 Citations

12 ☐ Preliminary Amendment

13 ☐ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)

14 ☐ Small Entity ☐ Statement filed in prior application
Statement(s) Status still proper and desired

15 ☐ Certified Copy of Priority Document(s)
(if foreign priority is claimed)

16. ☐ Other

17 If a CONTINUING APPLICATION, check appropriate box and supply the requisite information

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. /

18. CORRESPONDENCE ADDRESS

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

5

Nicholas S. Gantenberg

Robert E. Singer

FIELD

The present invention relates to a novel therapeutic use of stilbenic
10 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

15 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
20 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
25 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
30 dextromethorphan, expectorants such as guaifenesin and antipyretics such
as acetaminophen. In an attempt to improve existing cold remedies, experts

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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 Alpha₂ 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 Bradykinin 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 RE033,485 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

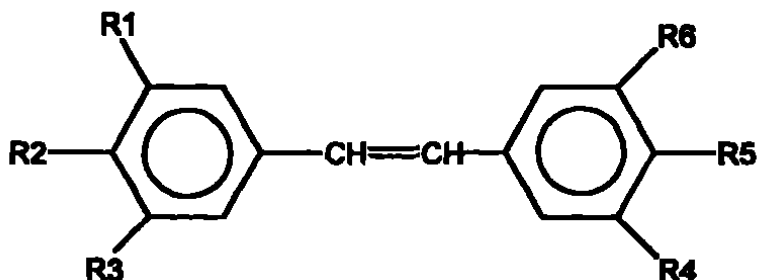
Phytoalexins are defense substances with antimicrobial properties which are produced by plants after infections. They include various groups of natural substances (e.g., isoflavonoids, terpenoids, polyacetylenes and dihydrophenanthrenes). Different sources of phytoalexin include the roots of *Veratrum 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. Resveratrols 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 218-220, 1997). The dietary supplement Huzhang, a source of resveratrol, is reported to have antioxidant properties (product label for Resveratrol from "Source Naturals," 1997).

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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 R¹, R², R³, R⁴, R⁵, and R⁶ 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

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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 luminal 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

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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, Hildeberg, O., Acoustic reflections during rhinometry: spatial resolution and sound loss, 84(3) J. Appl. Physiol. 1030-9, 1998, Hildeberg, 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.

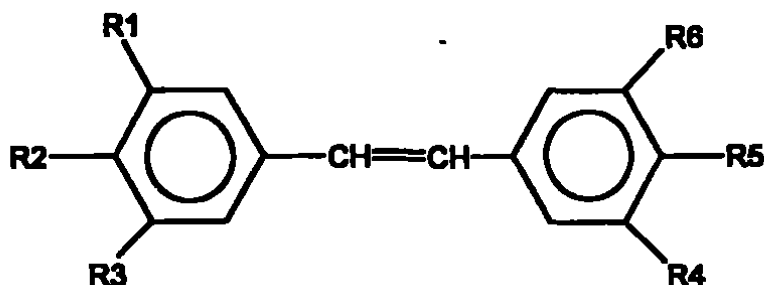
A. Method

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

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administering to a subject a composition including a stilbenic phytoalexin having the following chemical Formula 1



Formula 1

where R¹, R², R³, R⁴, R⁵, and R⁶ 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 R¹, R³, R⁵, and are hydroxyl and R², R⁴, and R⁶ 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, Daxchlorpheniramine, Clemastine, Diphenhydramine, Azelastine, Acrivastine, Levocarbastine, Mequitazine, Astemizole, Ebastine, Loratadine, Cetirizine, Terfenadine, Promethazine, Dimenhydrinate, Mecizine, 5 Tripelennamine, Carbinoxamine, Cyproheptadine, Azatadine, Brompheniramine, Tnprolidine, Cyclizine, Thonzylamine, Pheniramine, and mixtures thereof.

Antitussives, including, Hydrocodone, Noscapine, Benzonatate, Diphenhydramine, Chlorphedianol, Clobutanol, Fominoben, Glaucone, 10 Pholcodine, Zipeprol, Hydromorphone, Carbetapentane, Caramiphen, Levopropoxyphene, Codeine, Dextromethorphan, and mixtures thereof

Antiinflammatories, preferably Non-Steroidal Anti-Inflammatories (NSAIDS) including, Ketoprofen, Indoprofen, Indomethacin, Sulindac, Dflunisal, Ketorolac, Piroxicam, Meclofenamate, Benzydamine, Carprofen, 15 Diclofenac, Etodolac, Fenbufen, Fenoprofen, Flurbiprofen, Mefenamic, Nabumetone, Phenylbutazone, Pirofen, Tolmetin, Ibuprofen, Naproxen, Sodium naproxen, Aspirin, and mixtures thereof.

Analgesics, including, Acetaminophen

Expectorants/Mucolytics, including, Ambroxol, Bromhexine, Terpin, 20 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.

25 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, 30 Beclomethasone, Fluticasone, Budesonide, Mometasone, Triamcinolone,

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Dexamethasone, Flunisolide, Prednisone, Hydrocortisone and mixtures thereof

Bronchodilators, preferably for inhalation, including, Albuterol, Epinephrine, Ephedrine, Metaproterenol, Terbutaline, Isoetharine, 5 Terbutaline, Isoetharine, Pirbuterol, Bitolterol, Fenoterol, Rimiterol, Ipratropium, and mixtures thereof

Antivirals, including, Amantadine, Rimantadine, Envirodine, Nonoxonols, Acyclovir, Alpha-Interferon, Beta-Interferon, and mixtures thereof

10 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 15 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 20 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, anthocyanins, 25 anthocyanosides, carotenoids, bioflavonoids, 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 30 mixtures thereof

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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

5 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
10 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

	Example 1	Example 2
15 <u>Ingredients</u>	<u>(Wt. %)</u>	<u>(Wt. %)</u>
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
20 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	—
25 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.

30

Examples 3 and 4

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

09364944.0730 9

09364944-073099

		Example 3	Example 4
	<u>Ingredients</u>	<u>(Wt. %)</u>	<u>(Wt. %)</u>
	Cetylpyridinium Chloride	0 045	0 045
	Domiphen Bromide	0 005	0 005
5	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
10	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	—
15	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
20	Purified water	q s	q s

Example 5

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

	<u>Ingredients</u>	<u>(Wt. %)</u>
	Resveratrol	1 00
	Flavor	0 10
	Polysorbate 80	0 25
30	Saccharin Sodium	0 05
	Methylparaben	0 20
	Propylparaben	0 10
	Water	q s

35

Example 6

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

	<u>Ingredients</u>	<u>(Wt. %)</u>
5	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
10	Purified Water	q.s.

Example 7

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

	<u>Ingredient</u>	<u>Grams</u>
15	Resveratrol	1.0
	Nonionic detergent ¹	0.70
	Dibasic sodium phosphate	0.11
	Monobasic potassium phosphate	0.38
20	Benzalkonium chloride	0.04
	Chlorhexidine gluconate	0.28
	Disodium EDTA	0.01
	Flavoring ²	
	Camphor and eucalyptol ³	

25 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.

30 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

09364944.0730 9

about 5 to 500 microliters of solution into each nostril. Repeat three times daily

Example 8

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

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

1 Available as Pluronic 127 from BASF Corporation

20 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.

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Example 9

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

<u>Ingredients</u>	<u>Grams</u>
Resveratrol	5 0
5 Dextrose powder	1 0
Ethanol	1 0
Flavoring ¹	
camphor and eucalyptol ²	
Lactose powder QS to 100 grams	
10 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.
- 15 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
- 20 times daily.

Example 10

An example of an inhalant is made by mixing the following

<u>Ingredients</u>	<u>Grams</u>
Resveratrol	0 80
25 Sorbitan trioleate	0 40
Propellant 114 ¹	49 50
Propellant ²	49 51
1 Freon 114 E I Dupont	
2 Freon 12 E.I. Dupont	

- 30 Micronize the resveratrol in a fluid energy mill at 100 pounds per square inch pressure. Dissolve the sorbitan trioleate in the mixed

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64

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

5

Example 11

An example of sublingual tablet made by mbdng the following

	<u>Ingredients</u>	<u>Grams</u>
	Resveratrol	10
10	Lactose	86
	Sucrose	87
	Acacia	10
	Talc	6
	Magnesium stearate	1
15	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 dned 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.

20

Example 12

An example of sublingual tablet made by mixing the following

25	<u>Ingredients</u>	<u>Grams</u>
	Resveratrol	4 4
	Lactose	32 25
	Polyethylene glycol	0 35
	Alcohol-water (60 40)	q.s.

30

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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.

5

Example 13

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

	<u>Ingredients</u>	<u>Grams</u>
10	Resveratrol	5
	Ethanol	80
	Mineral oil	12
	Hydroxypropyl cellulose	2
	Menthol	1
15	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 phytoalexans of Formula 1 on symptoms, are believed to be attributable, in part, to increased general respiratory health.

20

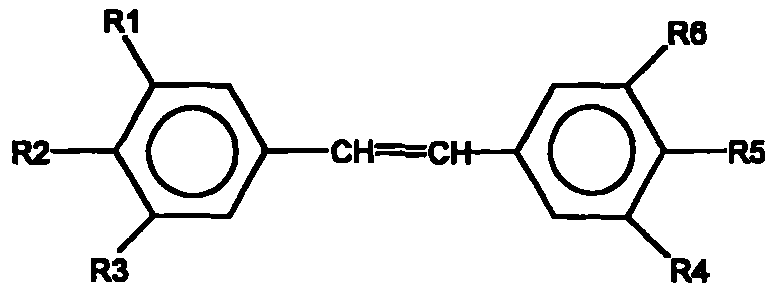
While the invention has been described in terms of its preferred embodiments, those skilled in the art will recognize that the invention can be practiced with considerable modification within the spirit and scope of the appended claims.

25

WHAT IS CLAIMED IS

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1 A method for the prophylaxis and treatment of cold and influenza-like symptoms comprising administering to a subject a composition including a stilbenic phytoalexin having the structure



5 wherein R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen and hydroxy; and medicinally acceptable salts or esters thereof

2 The method of Claim 1 wherein the stilbenic phytoalexin is a trihydroxystilbene or tetrahydroxystilbene

3 The method of Claim 2 wherein the stilbenic phytoalexin is 3,4',5-trihydroxystilbene resveratrol

4 The method of Claim 1 wherein the composition comprises from about 0.01% to about 99.99% of the stilbenic phytoalexin.

5 The method of Claim 4 wherein the composition further comprises natural source products, natural source extracts, or natural source powders of the stilbenic phytoalexin

6 The method of Claim 4 wherein the composition is a herbal medicament.

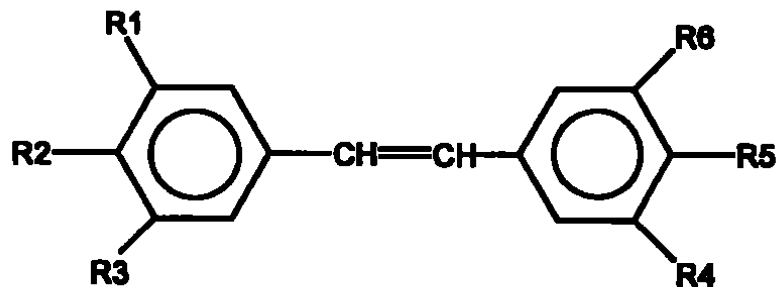
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7 The method of Claim 4 wherein the composition is a solid, semi-solid, liquid, or semi-liquid, in the form of powders, granules, lyposomes, tablets, capsules, gels, lozenges, dentifrices, and mouthwashes.

8 The method of Claim 4 wherein the composition further comprises an enhancing agent selected from the group consisting of herbs, phenols, polyphenols, anthocyanins, anthocyanosides, carotenoids, bioflavonoids, vitamins, mineral salts, metal ions, antioxidants, vegetal fibers, and mixtures thereof

9 The method of Claim 4 wherein the composition comprises a pharmaceutical agent selected from the group consisting of antihistamine, antitussive, antiinflammatory, analgesic, mast cell stabilizer, leukotriene antagonist, methoxyanthine, antioxidant, steroid, bronchodilator, antiviral, biologic, and mixtures thereof

10 A method for the prophylaxis and treatment of congestion associated with respiratory afflictions comprising administering to a subject a composition including a stilbenic phytoalexin having the structure:



5 wherein R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen and hydroxy; and medicinally acceptable salts or esters thereof

11. The method of Claim 10 wherein the stilbenic phytoalexin is a trihydroxystilbene or tetrahydroxystilbene

12 The method of Claim 11 wherein the stilbenic phytoalexin is 3,4',5-trihydroxystilbene resveratrol

13 The method of Claim 10 wherein the composition comprises from about 0.01% to about 99.99% of the stilbenic phytoalexin

14 The method of Claim 13 wherein the composition further comprises natural source products, natural source extracts, or natural source powders of the stilbenic phytoalexin

15 The method of Claim 13 wherein the composition is a herbal medicament.

16 The method of Claim 13 wherein the composition is a solid, semi-solid, liquid, semi-liquid in the form of powders, granules, liposomes, tablets, capsules, gels, lozenges, dentifrices, and mouthwashes

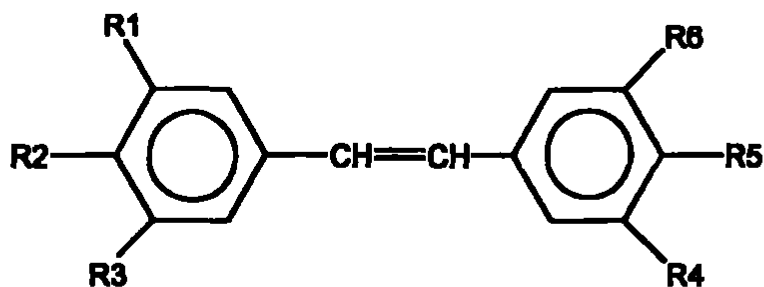
17 The method of Claim 13 wherein the composition further comprises an enhancing agent selected from the group consisting of herbs, phenols, polyphenols, anthocyanins, anthocyanosides, carotenoids, bioflavonoids, vitamins, mineral salts, metal ions, antioxidants, vegetal fibers, and mixtures thereof

18 The method of Claim 13 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.

19 A composition comprising:

a) a stilbenic phytoalexin having the structure

09364944-073099



wherein R¹, R², R³, R⁴, R⁵, and R⁶ are independently selected from hydrogen and hydroxy, and medicinally acceptable salts or esters thereof; and

- b) 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

5

20 The composition of Claim 19 wherein the stilbenic phytoalexin is 3,4',5-trihydroxystilbene resveratrol

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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.

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Attorney-in-fact
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Signature of Attorney-in-fact

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DECLARATION COMBINED WITH POWER OF ATTORNEY

Page 1 of 2

Attorney Docket No. 7690

As a below named inventor, I hereby declare that.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled Composition for Prophylaxis and Treatment of Symptoms Associated with Cold and Influenza-Like Illnesses and Their Methods of Use the specification of which

(check one) ☒ is attached hereto.
☐ was filed on _____ as U.S. Application
Serial No. or PCT Int'l Application No. _____
and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37 Code of Federal Regulations §1.56

I hereby claim foreign priority benefits under Title 35 United States Code §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one other country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed

Prior Foreign Application(s)		Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes ☐ No

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below

Application Serial No.	Filing Date	Application Serial No.	Filing Date
------------------------	-------------	------------------------	-------------

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT International application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
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As named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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