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12 -
Bogotá D.C., 10 de mayo de 2018

Señor
Pablo Felipe Robledo Del Castillo
Superintendente
Superintendencia de Industria y Comercio
Ciudad.-

Tengo el agrado de dirigirme a usted con relación a una solicitud de patente del recurso biológico *Croton lechleri* (sangre de grado), presentada ante la Superintendencia de Industria y Comercio por JAGUAR ANIMAL HEALTH con número NC2017/0007823 con fecha de publicación 05 de enero de 2017, titulada "Composiciones para tratar la diarrea en animales de compañía".

Sobre el particular, la Comisión Nacional para la Protección al Acceso a la Diversidad Biológica Peruana y a los Conocimientos Colectivos de los Pueblos Indígenas del Perú – creada por Ley N° 28246 y adscrita a la Presidencia del Consejo de Ministros – considera que dicha solicitud de patente es indebida por no cumplir con el requisito de Nivel Inventivo exigido por Régimen Común sobre Propiedad Industrial de la Comisión de la Comunidad Andina. En ese sentido, se adjunta el informe respectivo con el fin de expresar la oposición del Estado Peruano a la mencionada solicitud de patente.

Sin otro particular, hago propicia la oportunidad para expresarle a usted las seguridades de mi más alta y distinguida consideración.


Ignacio Higuera Hare
Embajador



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DOCUMENTO DE OPOSICIÓN CONTRA UNA SOLICITUD DE PATENTE COLOMBIANA

Número de solicitud: NC2017/0007823
Fecha de solicitud: 01-08-2017
Fecha de publicación: 05-01-2018
Prioridades: US 62/101,663 de fecha 09/01/2015
US 62/117,927 de fecha 18/02/2015
Título: COMPOSICIONES PARA TRATAR LA DIARREA EN ANIMALES DE COMPAÑÍA
Solicitante: JAGUAR ANIMAL HEALTH
Opositor: Comisión Nacional para la Protección al acceso a la diversidad biológica peruana y a los Conocimientos Colectivos de los Pueblos Indígenas - Perú

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1. Solicitud

Por medio de la presente se solicita se deniegue la Solicitud de Patente N° NC2017/0007823, en el alcance de todas las reivindicaciones. Los motivos que apoyan dicha solicitud se presentan en la declaración que figura a continuación.

2. Acceso a Recursos Genéticos

Las Disposiciones complementarias de la Decisión 391 del Régimen Común sobre Acceso a los Recursos Genéticos, establece que:

SEGUNDA. - Los Países Miembros no reconocerán derechos, incluidos los de propiedad intelectual, sobre recursos genéticos, productos derivados o sintetizados y componentes

intangibles asociados, obtenidos o desarrollados a partir de una actividad de acceso que no cumpla con las disposiciones de esta Decisión (...)."

TERCERA.- Las oficinas nacionales competentes en materia de Propiedad Intelectual exigirán al solicitante la indicación del número del registro del contrato de acceso y copia del mismo, como requisito previo para la concesión del respectivo derecho, cuando tengan certeza o indicios razonables de que los productos o procesos cuya protección se solicita han sido obtenidos o desarrollados a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen(...)."¹

Además, el Régimen Común sobre Propiedad Industrial de la Comisión de la Comunidad Andina, menciona que el solicitante debe presentar la copia del contrato de acceso al recurso genético, cuando el producto o procedimiento, objeto de una solicitud de patente de invención, ha sido obtenido o desarrollado a partir de un recurso genético o producto derivado del cual cualquiera de los Países Miembros de la Comunidad Andina es país de origen, de acuerdo a lo establecido en el artículo 26, literal (h) de la Decisión 486 de la Comisión de la Comunidad Andina.

En este sentido, se observa que la solicitud de patente NC2017/0007823 está referida al recurso sangre de grado (*Croton lechleri*), la cual es una especie compartida con los países miembros de la Comunidad Andina, por lo que el solicitante debe cumplir con la presentación del contrato de acceso a dicho recurso genético.

3. Documentos citados en la Oposición

Tabla 1

Documento	Tipo	Detalles	Fecha de Publicación
D1	Documento de Patente	US 2005/0019389 (PS PHARMACEUTICAL INC) Titulado: "Enteric formulations of proanthocyanidin polymer antidiarrheal compositions" con fecha de publicación 27-01-2005.	2005
D2	Documento de patente	US 8,709,515 (Colitz C. et al) Titulado "Nutritional supplement method" con fecha de publicación 29 de abril de 2014	2014

Documento D1 describe un método para el tratamiento de diarrea acuosa o secretora en animales de compañía. El párrafo [0028] describe una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de un agente que comprende una composición de polímero de proantocianidina preparada a partir de *Croton* spp, preferiblemente *Croton lechleri*. En el párrafo [0092] se indica que la formulación farmacéutica de la invención puede ser también incorporada en animales con diarrea secretora tales como animales bovino, canino, felino, entre otros. En el párrafo [139], se describe un método para la formulación de gránulos con recubrimiento entérico o partículas pulverizadas de polímeros de proantocianidina (microesferas de 300µ a 500µ).

¹ Normativa vigente de Acceso: Decisión 391, Régimen de Acceso a los Recursos Genéticos.

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Documento D2 describe que las proantocianidinas tienen un rango amplio de actividades biológicas tales como propiedades antimicrobianas (Columna 7 línea 17). En el ejemplo 2 se describe una forma de dosificación sólida saborizada y masticable que combina ingredientes activos con saborizantes utilizadas como alimento comercial para perros que son adicionados para incrementar la palatabilidad del producto.

4. Alcance de la solicitud de patente cuestionada

El pliego reivindicaciones presentado ante la Superintendencia de Industria y Comercio del Gobierno de Colombia, con fecha 28 de diciembre de 2017, comprende 32 reivindicaciones donde:

La reivindicación independiente 1 define *"Un método para tratar la diarrea acuosa o secretora en un animal de compañía no humano, tal método comprende administrar de forma oral al animal que lo necesita, una composición recubierta entérica o no entérica que comprende el polímero de proantocianidinas soluble acuoso de Croton lechleri en una forma de dosificación sólida, saborizada y masticable y en una cantidad eficaz para tratar la diarrea en el animal de compañía"*.

La reivindicación independiente 2 define *"Un método para tratar la diarrea inducida por quimioterapia (CID) en un animal de compañía canino, tal método comprende administrar por vía oral al animal que lo necesita, una composición recubierta entérica o no entérica que comprende el polímero de proantocianidinas soluble acuoso de Croton lechleri en una forma de dosificación sólida, saborizada y masticable y en una cantidad eficaz para tratar la CID en el animal de compañía"*

Las reivindicaciones 3 a 32 son dependientes de la reivindicación 1 ó 2.

5. No invenciones y excepciones a la patentabilidad:

Para el examen de patentabilidad del pliego de reivindicaciones se tomará en cuenta lo señalado en el artículo 20 - literal d) de la Decisión 486 de la Comisión de la Comunidad Andina, que señala que solo se considera patentable los productos o procedimientos y no los métodos terapéuticos.

En ese sentido se observa que las reivindicaciones 1 a 32 describen un método terapéutico, tal como se observa a continuación:

La reivindicación 1 define *"Una composición que comprende el polímero de proantocianidinas soluble acuoso de Croton lechleri para uso en el tratamiento de la diarrea acuosa o secretora en un animal de compañía no humano, en donde dicha composición es para administración oral y está en una forma de dosificación sólida, saborizada y masticable"*.

La reivindicación 2 define *"Una composición que comprende el polímero de proantocianidinas soluble acuoso de Croton lechleri para uso en el tratamiento de la diarrea inducida por quimioterapia (CID) en un animal de compañía no humano, en donde dicha composición es para administración oral y está en una forma de dosificación sólida, saborizada y masticable"*.

Considerando que a lo largo de la memoria descriptiva y en el pliego de reivindicaciones se hace referencia a que la composición se administrará en cantidades (2mg/kg a 4mg/kg) y frecuencias (dos veces al día, durante tres días, etc), ambas reivindicaciones involucran un método para el tratamiento

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de la diarrea, por lo que NO SON PATENTABLES de acuerdo a la Decisión 486 de la Comisión de la Comunidad Andina que establece:

Artículo 20.- No serán patentables:

d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.

Del mismo modo, las reivindicaciones dependientes 3 a 32 que definen características particulares del método de tratamiento descrito en las reivindicaciones 1 o 2, tampoco serían patentables, considerando que aluden directamente a la periodicidad en la que se administra la composición y a la cantidad del principio activo empleado (mg/Kg), habiéndose verificado que el concepto de "dosificación" no adquiere significado a partir de los excipientes o demás características técnicas de una composición sino de la farmacocinética o biodisponibilidad que tenga el principio activo.

6. Usos

La resolución del Tribunal de Justicia de la Comunidad Andina en el Proceso 89-AI-2000 publicada en la Gaceta Oficial N° 722 del 12 de octubre de 2001, que interpreta el artículo 1 de la Decisión 344 equivalente al artículo 14 de la Decisión 486: "Los Países Miembros otorgarán patentes para las invenciones sean de PRODUCTOS o de PROCEDIMIENTOS en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial", por lo que no puede desprenderse del texto de este artículo, la posibilidad de patentamiento de otra clase o naturaleza de creaciones distintas a las invenciones, como por ejemplo los USOS o, concretamente, los segundos usos.

De acuerdo al párrafo precedente se observa que las reivindicaciones 1 y 2 describen el uso de una composición al hacer referencia a: "*Una composición que comprende el polímero de proantocianidinas soluble acuoso de Croton lechleri para uso en el tratamiento de...*"

Las reivindicaciones 3 a 32 figuran como dependientes de la cuestionada reivindicación 1 o 2, por lo que también implican usos.

En ese sentido, las reivindicaciones 1 y 2 y sus reivindicaciones dependientes 3 a 32 no son susceptibles de patentarse según el Artículo 14 de la Decisión 486 y su interpretación por el Tribunal de Justicia de la Comunidad Andina a la luz del Proceso N° 89-AI-2000 publicada en la Gaceta Oficial N° 722 con fecha 12 de octubre del 2001, que solamente considera patentables los productos o procedimientos, pero no los usos.

7. Novedad:

Una composición farmacéutica que comprende el polímero de proantocianidinas soluble de *Croton lechleri* en una forma de dosificación sólida, saborizada y masticable, no se encontraría anticipada por los documentos D1 y D2 toda vez que ninguno de dichos documentos revela específicamente dicha forma de dosificación.

8. Ausencia de Nivel Inventivo:

En vista del estado de la técnica anteriormente citado, el problema que se pretende resolver en la solicitud consiste en proveer una composición para el tratamiento de la diarrea acuosa o secretora en un animal de compañía.

La solución propuesta consiste en proveer una formulación saborizada que comprende polímeros de proantocianidinas de *Croton lechleri* tal como se define en las reivindicaciones 1 ó 2.

Los documentos D1 y D2 son considerados los más cercanos del estado de la técnica descrito en las reivindicaciones 1 y 2.

Documento D1 describe un método para el tratamiento de diarrea acuosa o secretora en animales de compañía, que comprende una composición farmacéutica a base del polímero de proantocianidina obtenida a partir de *Croton lechleri*.

Documento D2 describe que las proantocianidinas obtenidas a partir *Croton lechleri* presentan propiedades antimicrobianas y son empleadas junto a saborizantes en la elaboración de formas de dosificación saborizadas y masticables para el desarrollo de alimento comercial para perros.

De la revisión de los documentos citados se considera que la solicitud de patente NC2017/0007823 no cumple con el requisito de nivel inventivo, establecido en el Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina, por las siguientes razones:

El documento D1 describe un método para el tratamiento de la diarrea acuosa o secretora en un animal de compañía, donde el método consiste en la administración de una composición de cubierta entérica o no entérica de un polímero de proantocianidina obtenido a partir de *Croton lechleri*, sin embargo, dicho documento no describe específicamente que la composición se presente en una forma de dosificación sólida saborizada y masticable. Al respecto, el documento D2 sí hace referencia a formas de dosificación sólida saborizada y masticable para ser utilizada en animales. En vista que ambos documentos, D1 y D2 describen el uso de proantocianidinas en animales, hubiera sido obvio para un experto en el arte combinar las enseñanzas de los documentos D1 y D2 y diseñar la composición que comprenda el polímero de proantocianidinas soluble de *Croton lechleri* en una forma de dosificación sólida, saborizada y masticable para el tratamiento de diarreas en animales, como se pretende proteger en la presente solicitud.

Asimismo, en el caso se desarrolle una composición específica de una materia ya divulgada en el estado de la técnica, resulta necesario que el solicitante proporcione ventajas inesperadas o efectos sorprendentes o argumentos convincentes, presentando resultados de ensayos comparativos con la técnica anterior más cercana, sin embargo, estos requerimientos no se reflejan en la presente solicitud de patente.

En consecuencia, la composición que se pretendería proteger en las reivindicaciones 1 y 2, carecen de nivel inventivo a la luz de la combinación de lo divulgado en los documentos D1 y D2. Del mismo modo las reivindicaciones 3 a 32 tampoco cumplirían con el requisito de nivel inventivo, al ser dependientes de las reivindicaciones 1 y 2 cuestionadas.

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9. Resumen

En base a los motivos de oposición expuestos anteriormente, las reivindicaciones 1 a 32 no se consideran invenciones y no cumplen con el requisito de actividad inventiva considerando los documentos D1 y D2; de modo que la solicitud de patente NC2017/0007823 debe ser denegada.

**The National Commission for the Protection of Access
to Peruvian Biological Diversity and
to the Collective Knowledge of Indigenous Peoples
PERÚ**

Adjunto:

Copia de los datos bibliográficos: NC2017/0007823

Documento de técnica anterior D1 y D2



Espacenet

Bibliographic data: WO2016112312 (A1) — 2016-07-14

METHODS OF TREATING DIARRHEA IN COMPANION ANIMALS

Inventor(s): MARTINOD SERGE [US] ± (MARTINOD, SERGE)

Applicant(s): JAGUAR ANIMAL HEALTH [US] ± (JAGUAR ANIMAL HEALTH)

Classification: - international: A01N65/00

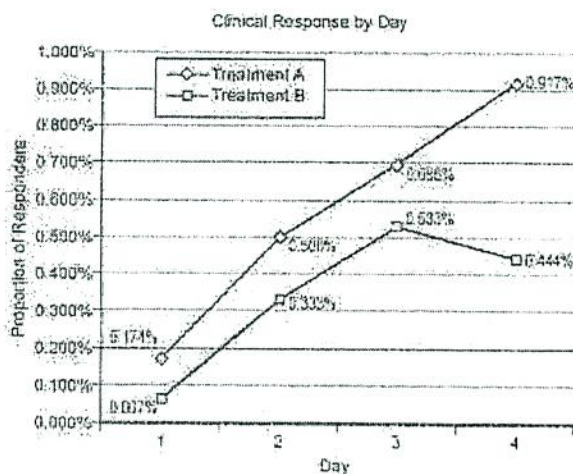
- cooperative: A61K36/47

Application number: WO2016US12681 20160108 Global DossierPriority number(s): US201562101663P 20150109 ; US201562117927P 20150218Also published as: AU2016205145 (A1), CA2972996 (A1), CN107106536 (A), EP3242557 (A1), KR20170103834 (A), more

Abstract of WO2016112312 (A1)

Provided are methods and compositions for treating diarrhea, particularly secretory diarrhea, watery diarrhea and chemotherapy induced diarrhea (CID), in young and adult non-human companion animals, such as dogs and cats, with a therapeutically effective amount of a proanthocyanidin polymer from *Croton lechleri*, in either enteric or non-enteric form.

FIG. 2





Espacenet

Bibliographic data: US2005019389 (A1) — 2005-01-27

Enteric formulations of proanthocyanidin polymer antidiarrheal compositions

Inventor(s): ROZHON EDWARD JAMES [US]; KHANDWALA ATUL S [US]; SABOUNI AKRAM [US]; BALWANI GUL P [US]; CHAN JODY WAI-HAN [US]; SESIN DAVID F [US] ± (ROZHON EDWARD JAMES, ; KHANDWALA ATUL S, ; SABOUNI AKRAM, ; BALWANI GUL P, ; CHAN JODY WAI-HAN, ; SESIN DAVID F)

Applicant(s): PS PHARMACEUTICAL INC [US] ± (PS PHARMACEUTICAL, INC, ; NAPO PHARMACEUTICALS, INC)

Classification: - international: A61K31/352; A61K31/353; A61K31/765; A61K36/18; A61K47/32; A61K9/10; A61K9/28; A61K9/32; A61K9/50; A61K9/54; A61K9/58; A61P1/12; A61P31/04; C07D311/62; (IPC1-7): A61K31/353; A61K31/7048; A61K35/78; A61K9/48
- cooperative: A61K31/353; A61K31/765; A61K9/2846; A61K9/5078; Y10S514/867

Application number: US20040919969 20040817 Global Dossier

Priority number(s): US20040919969 20040817 ; US20000712033 20001114 ; US19980066989 19980423 ; US19960730772 19961016

Also published as: AT430477 (T); AU4988197 (A); CA2269078 (A1); CA2269078 (C); DK0935417 (T3); more

Abstract of US2005019389 (A1)

Pharmaceutical compositions containing a proanthocyanidin polymer composition which are useful for the treatment and prevention of secretory diarrhea are provided. The invention specifically relates to pharmaceutical formulations of a proanthocyanidin polymer composition which has been isolated from a *Croton* spp. or a *Calophyllum* spp. In particular, the invention relates to a formulation of a proanthocyanidin polymer composition which protects the composition from the effects of stomach acid after oral administration, particularly to those formulations which are enteric coated. The invention also relates to methods of producing a directly compressible proanthocyanidin polymer composition, as well as compositions containing the directly compressible proanthocyanidin polymer composition.



US 20050019389A1

(19) United States

(12) Patent Application Publication

Rozhon et al.

(10) Pub. No.: US 2005/0019389 A1

(43) Pub. Date: Jan. 27, 2005

(54) ENTERIC FORMULATIONS OF
PROANTHOCYANIDIN POLYMER
ANTIDIARRHEAL COMPOSITIONS09/066,989, filed on Apr. 23, 1998, now abandoned,
which is a continuation-in-part of application No.
08/730,772, filed on Oct. 16, 1996, now abandoned.(75) Inventors: Edward James Rozhon, El Granada,
CA (US); Atul S. Khandwala, San
Carlos, CA (US); Akram Sabouni,
Fairport, NY (US); Gul P. Balwani,
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F. Sesin, San Carlos, CA (US)

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(52) U.S. Cl. 424/452; 424/725; 514/27;
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(21) Appl. No.: 10/919,969

(22) Filed: Aug. 17, 2004

Related U.S. Application Data

(60) Division of application No. 09/712,033, filed on Nov.
14, 2000, which is a continuation of application No.

(57) ABSTRACT

Pharmaceutical compositions containing a proanthocyanidin polymer composition which are useful for the treatment and prevention of secretory diarrhea are provided. The invention specifically relates to pharmaceutical formulations of a proanthocyanidin polymer composition which has been isolated from a Croton spp. or a Calophyllum spp. In particular, the invention relates to a formulation of a proanthocyanidin polymer composition which protects the composition from the effects of stomach acid after oral administration, particularly to those formulations which are enteric coated. The invention also relates to methods of producing a directly compressible proanthocyanidin polymer composition, as well as compositions containing the directly compressible proanthocyanidin polymer composition.

[0021] It has been shown that Sangre de Drago from *Croton dracooides* and from *Croton lechleri* contains an alkaloid identified as taspine, which exhibits anti-inflammatory activity (Persinos et al., 1979, *J. Pharm. Sci.*, 68:124). Taspine has also been shown to inhibit RNA-directed DNA polymerase activity in the avian myeloblastosis virus, Rauscher leukemia virus and Simian sarcoma virus (Sethi, 1977, *Canadian J. Pharm. Sci.*, 12:7).

[0022] A variety of phenolic and diterpene compounds isolated from Sangre de Drago were tested for their antitumor, antibacterial and wound healing properties (Chen et al., *Planta Med.*, 60:541). The proanthocyanidins in the sap were found to have little antitumor or antibacterial activity and slight wound healing activity.

[0023] U.S. Pat. No. 5,211,944 first described the isolation of an aqueous soluble proanthocyanidin polymer composition from *Croton* spp. and the use of the composition as an antiviral agent (See also Ubillas et al., 1994, *Phytomedicine*, 1:77). The proanthocyanidin polymer composition was shown to have antiviral activity against a variety of viruses including, respiratory syncytial, influenza, parainfluenza and herpes viruses.

[0024] *Calophyllum inophyllum* is a tree ranging from India to East Africa to Polynesia. Seed oil is used in folk medicine as an antiparasitic in treatment of scabies, ringworm and dermatosis as well as other uses such as analgesia. In Indo-China, the powdered resin is used for ulcers and wound healing. In Indonesia, the bark is applied externally to treat swollen glands and internally as a diuretic. The sap is used as an emollient for chest pain as well as for tumors and swelling. Leaf extracts are used as a wash for inflamed eyes. The Cambodians use leaf extracts in inhalations for treatment of vertigo and migraine. The Samoans use the sap as an arrow poison.

[0025] U.S. Pat. No. 5,211,944 also discloses the isolation of an aqueous soluble proanthocyanidin polymer composition from *Calophyllum inophyllum* and the use of this composition as an antiviral agent.

[0026] It has been determined that the proanthocyanidin polymer compositions of the invention are acid labile and subject to inactivation by the acidic environment of the stomach. Before the present application, no disclosure has been made of a pharmaceutical composition of a proanthocyanidin polymer composition isolated from either *Croton* spp. or *Calophyllum* spp. which protects the proanthocyanidin polymer composition from the acidity of gastric fluid so that the proanthocyanidin polymer composition can be administered orally for treatment of secretory diarrhea.

[0027] The need remains for an effective pharmaceutical composition, the administration of which will reduce the ion efflux into the gut elicited by secretory diarrhea. Such an agent would be useful to prevent the fluid and electrolyte loss and dehydration caused by secretory diarrhea. The object of the present invention is to provide an effective pharmaceutical formulation of an antidiarrheal agent which will fulfill this need, and specifically to provide a pharmaceutical formulation which will protect the antidiarrheal agent from the acidity of the stomach as well as methods for treating diarrhea using the pharmaceutical formulation.

3. SUMMARY OF THE INVENTION

[0028] The present invention relates to pharmaceutical compositions comprising a therapeutically effective amount

of an antidiarrheal agent comprising a proanthocyanidin polymer composition. The proanthocyanidin polymer composition is preferably prepared from a *Croton* spp., preferably *Croton lechleri*. The proanthocyanidin polymer composition can also be prepared from a *Calophyllum* spp., in particular *Calophyllum inophyllum*.

[0029] The pharmaceutical compositions of the invention are formulated to protect the proanthocyanidin polymeric composition from degradation by the acidic conditions of the stomach and from interactions with proteins, such as pepsin, present in the stomach. In a preferred embodiment, the proanthocyanidin polymer composition is enteric coated. In a more preferred embodiment, the pharmaceutical composition contains a proanthocyanidin polymer composition that can be directly compressed into a tablet. As used herein "directly compressible" means that a proanthocyanidin polymer composition, in the absence of any excipients, additives, diluents, etc., that improve compressibility, can be directly pressed into a tablet having a pharmaceutically suitable hardness, i.e., a hardness (also referred to as "crushing strength") greater than 6 kp, and friability, i.e., a friability of no more than 1% loss in weight. Preferably, the directly compressible proanthocyanidin polymer composition is directly compressed (optionally in the presence of a lubricant such as, but not limited to, magnesium stearate) into a tablet of pharmaceutically suitable hardness and friability, and is subsequently enterically coated.

[0030] Whether a proanthocyanidin polymer composition can be directly compressed into a tablet of pharmaceutically acceptable hardness and friability can be determined by any method known in the art, for example by compressing a formulation into a tablet and determining its hardness and friability by known methods, e.g., as described in Sections 5.1 and 10, *infra*. To be pharmaceutically acceptable, a tablet has a hardness greater than 6 kp (but preferably a hardness of 8-14 kp, more preferably 10-13 kp) and a friability of not more than 1% loss in weight (but preferably a friability of not more than 0.8% loss in weight, and more preferably a friability of not more than 0.5% loss in weight).

[0031] In another preferred embodiment, the proanthocyanidin polymer composition is provided in combination with a substance able to reduce the secretion of stomach acid or able to reduce the acidity of stomach fluid.

[0032] The present invention also encompasses methods for treating diarrhea, particularly secretory diarrhea, in warm blooded animals, including humans, comprising administering, to a non-human animal or human suffering from diarrhea, a pharmaceutical composition comprising a therapeutically effective amount of a proanthocyanidin polymer composition isolated from a *Croton* spp., or a *Calophyllum* spp., or a pharmaceutically acceptable derivative thereof, formulated to protect the proanthocyanidin polymer composition from the stomach environment, e.g., from the action of stomach acid and interaction with proteins, such as pepsin, in the stomach and a pharmaceutically acceptable carrier. In addition, the present invention encompasses methods for treating secretory diarrhea in animals, including humans, comprising administering, to a non-human animal or human suffering from diarrhea, (a) a pharmaceutical composition comprising a therapeutically effective amount of a proanthocyanidin polymer composition isolated from a *Croton* spp., or a *Calophyllum* spp., or a pharmaceutically

acceptable derivative thereof, and a pharmaceutically acceptable carrier; and (b) a pharmaceutical composition either comprising an amount effective to inhibit stomach acid secretion of a compound that is effective to inhibit stomach acid secretion or comprising an amount effective to neutralize stomach acid of a compound that is effective to neutralize stomach acid, and a pharmaceutically acceptable carrier.

[0033] The present invention also provides methods for preventing diarrhea in warm blooded animals, including humans, comprising administering, to a non-human animal or human at risk of developing diarrhea, a pharmaceutical composition comprising a prophylactically effective amount of a proanthocyanidin polymer composition isolated from a *Croton* spp., or a *Calophyllum* spp., or a pharmaceutically acceptable derivative thereof, formulated to protect the proanthocyanidin polymer composition from the stomach environment, and a pharmaceutically acceptable carrier.

[0034] The present invention further relates to methods of producing a proanthocyanidin polymer composition that can be directly compressed, i.e. compressed without any excipients, into a tablet of pharmaceutically acceptable hardness and friability. In a preferred embodiment, the method of producing a proanthocyanidin polymer composition that can be directly compressed into a tablet comprises (1) extracting an aqueous solution of the latex from a *Croton* spp. with a short chain alcohol, preferably n-butanol; (2) concentrating the aqueous phase of the extracted material by ultrafiltration; (3) chromatographing the retentate from the ultrafiltration step on a cation exchange column, preferably a CM-Sephacrose column; (4) fractionating the material from the cation exchange column on a size exclusion column, preferably an LH-20 column; and (5) pooling the fractions collected from the size exclusion column that contain material with detectable absorbance at 460 nm. The invention also includes pharmaceutical compositions comprising the product of the process for producing a proanthocyanidin polymer composition that can be directly compressed into a tablet of pharmaceutically acceptable hardness and friability and methods of treating and preventing diarrhea in a human or non-human animal by administering a pharmaceutical composition containing the directly compressible proanthocyanidin polymer composition.

4. BRIEF DESCRIPTION OF THE FIGURES

[0035] FIG. 1. An overlay of HPLC chromatograms showing the chromatographic profiles of the proanthocyanidin polymer composition from *C. lechleri* after different treatments as UV absorption in milliabsorption units (mAU) over time of chromatography in minutes. The chromatogram graphed as a dotted line depicts the profile of the proanthocyanidin polymer composition after incubation in water ("in water"), the solid line depicts the proanthocyanidin polymer composition profile after incubation in HCl for 0.03 hours ("HCl after 0.03 h"), and the dashed line depicts the proanthocyanidin polymer composition from *C. lechleri* profile after incubation in HCl for 2.0 hours ("HCl after 2.0 h").

[0036] FIG. 2. A sample HPLC chromatogram of the proanthocyanidin polymer composition from *C. lechleri* after incubation in simulated gastric fluid at 37° C. for 0.03 hours. The chromatogram is graphed as UV absorption (mAU) over time in minutes.

[0037] FIG. 3. A sample HPLC chromatogram of the proanthocyanidin polymer composition from *C. lechleri* after incubation in simulated gastric fluid at 37° C. for 2 hours. The chromatogram is graphed as UV absorption (mAU) over time in minutes.

[0038] FIG. 4. A sample HPLC chromatogram of the proanthocyanidin polymer composition from *C. lechleri* after incubation in simulated gastric fluid at 37° C. for 2 hours, and followed by incubation for 4 more hours after dilution 1:1 in simulated intestinal fluid. The chromatogram is graphed as UV absorption (mAU) over time in minutes.

[0039] FIG. 5. A sample HPLC chromatogram of the proanthocyanidin polymer composition from *C. lechleri* after incubation in simulated gastric fluid at 37° C. for 2 hours, and followed by incubation for 6 more hours after dilution 1:1 in simulated intestinal fluid. The chromatogram is graphed as UV absorption (mAU) over time in minutes.

[0040] FIG. 6. Plot of the percentage of peak area ("Peak Area"), as calculated by dividing peak area of the HPLC profile of the proanthocyanidin polymer composition from *C. lechleri* in the test-medium by the peak area of the HPLC profile of the proanthocyanidin polymer composition in water and multiplying by 100, as a function of incubation time in hours. The line with open squares represents the % peak area of the proanthocyanidin polymer composition after incubation in SGF (simulated gastric fluid). The dotted line with diamonds represents the % peak area of the proanthocyanidin polymer composition after 2 hours of incubation in SGF and then dilution 1:1 into SIF (simulated intestinal fluid) for further incubation.

[0041] FIG. 7. This bar graph depicts the effect of the enteric coated formulation of the proanthocyanidin polymer composition from *C. lechleri* on intestinal fluid accumulation in mice exposed to cholera toxin. Results are presented as an average, for each group of mice A-C, of the fluid accumulation ratio in mg fluid/mg intestine. Mice in group A were treated only with water; mice in group B were treated with 131 mg enteric coated proanthocyanidin polymer composition in guar gum/kg; mice in group C were administered "EUDRAGIT™" and sugar with guar gum. The mice in all groups were evaluated at 7 hours after exposure to the cholera toxin. See Section 7, *infra* for details.

[0042] FIG. 8. This bar graph depicts the effect of the enteric coated formulation of the proanthocyanidin polymer composition from *C. lechleri* on intestinal fluid accumulation in mice exposed to cholera toxin. Results are presented as an average, for groups of mice A and B, of the fluid accumulation ratio in mg fluid/mg intestine. Mice in group A were treated with "EUDRAGIT™" and sugar in water, and mice in group B were treated with 131 mg enteric coated proanthocyanidin polymer composition/kg.

[0043] FIG. 9. This graph depicts the hardness (in kp) of 250 mg of the proanthocyanidin polymer composition compressed into tablets of varying thicknesses (in mm).

5. DETAILED DESCRIPTION OF THE INVENTION

5.1. Preparation of the Proanthocyanidin Polymer Composition

[0044] The proanthocyanidin polymer composition, effective for treatment of diarrhea, is comprised of monomeric

units of leucoanthocyanidins. Leucoanthocyanidins are generally monomeric flavonoids which include catechins, epicatechins, gallocatechins, galloepicatechins, flavanols, flavonols, and flavan-3,4-diols, leucocyanidins and anthocyanidins. The proanthocyanidin polymer composition useful for treating secretory diarrhea is comprised of polymers of 2 to 30 flavonoid units, preferably 2 to 15 flavonoid units, more preferably 2 to 11 flavonoid units and most preferably an average of 7 to 8 flavonoid units with a number average molecular weight of approximately 2500 Mn. The proanthocyanidin polymer composition is preferably soluble in an aqueous solution.

[0045] The proanthocyanidin polymer composition used in the present invention is preferably isolated from a *Croton* spp. or *Calophyllum* spp. by any method known in the art. For example, the proanthocyanidin polymer composition may be isolated from a *Croton* spp. or *Calophyllum* spp. by the method disclosed in U.S. Pat. No. 5,211,944 or in Ubillas et al. (1994, *Phytomedicine* 1: 77-106), both of which are incorporated herein by reference.

[0046] In a preferred embodiment, the proanthocyanidin polymer composition is directly compressed, that is, the proanthocyanidin polymer composition, without any excipients, can be compressed into a tablet, or other pharmaceutical formulation, that has a pharmaceutically acceptable hardness and friability. Whether a particular proanthocyanidin polymer composition is directly compressible can be determined by any method known in the art for determining the compressibility of a pharmaceutical substance (see, e.g., *Modern Pharmaceuticals*, Second Edition, Banker, G. S. and Rhodes, C. T. eds. (Marcel Dekker, Inc., New York (1990), pp. 417-419)). By way of example but not by way of limitation, compressibility may be determined by compressing a set amount of the proanthocyanidin polymer composition to be tested in a normal tableting machine, wherein sets of tablets are formed under increasing amounts in pressure. The greater the compression pressure, the thinner and harder the tablet will be. The hardness of the sets of tablets is then determined by a conventional hardness tester, which measures the amount of force just necessary to fracture the tablet. The hardness of the tablet formed will increase with the amount of pressure used to make the tablet, until the substance reaches the maximum hardness to which it can be compressed. Tablets compressed beyond this maximum point will not increase in hardness.

[0047] Preferably, the directly compressible proanthocyanidin polymer composition can be compressed into tablets having a hardness of greater than 6 kp (kiloponds), preferably a hardness of 8 to 14 kp, more preferably a hardness of 10 to 13 kp.

[0048] The ability for a proanthocyanidin polymer composition to be directly compressed can also be determined by measuring the friability of tablets formed from the proanthocyanidin polymer composition. The friability can be determined by conventional methods known in the art, such as the USP friability test (see USP 23, Tablet Friability <1216>). A directly compressible proanthocyanidin polymer composition can be compressed into a tablet that has a friability of not more than 1% loss in weight, preferably less than 0.8% loss in weight, more preferably less than 0.5% loss in weight.

[0049] In a preferred embodiment, the directly compressible proanthocyanidin polymer composition is isolated by the method described below:

[0050] Latex collected from *Croton lechleri* plants is mixed with purified water (preferably one part latex to two parts purified water) and then any insoluble material in the latex solution is allowed to settle, e.g., by leaving the mixture at 4° C. overnight (12 hours). The supernatant is pumped away from the residue and then extracted with a short chain alcohol, such as n-butanol, and preferably is extracted multiple times, more preferably three times. After each extraction, the alcohol phase is discarded and the aqueous phase retained. The aqueous phase is concentrated, for example, using an ultrafiltration device with a 1 kD cut-off membrane. This membrane can be a low protein binding cellulose membrane, or, alternatively, a polypropylene, teflon or nylon membrane can be used. The membrane used should be compatible with acetone. The purpose of the ultrafiltration is to remove the water from the material. The retentate from the ultrafiltration is then concentrated to dryness, for example using tray-dryers at approximately 37° C. ($\pm 2^\circ$ C.).

[0051] The dried material is subsequently dissolved in water and then chromatographed on a cation exchange column (for example, a CM-Sépharose column) and a size exclusion column (for example, an LH-20 column). In the preferred two column system, material is run over a CM-Sépharose and then an LH-20 column in a series.

[0052] Specifically, the dissolved material is loaded onto the cation exchange column and then washed with purified water. The proanthocyanidin polymer material is eluted from the cation exchange column with an aqueous acetone solution (preferably 30% acetone), thereby loading the proanthocyanidin polymer material onto the sizing column. The sizing column is disconnected from the cation exchange column and the material is then eluted off of the sizing column with an aqueous acetone solution (preferably 45% acetone). The fractions are collected and monitored with a UV detector, e.g., at a wavelength of 460 nm. Fractions containing the proanthocyanidin polymer material are combined and concentrated, for example, by ultrafiltration using, e.g., a 1 kD cut-off membrane (as described above for the ultrafiltration step prior to the chromatography steps). The retentate may then be concentrated to dryness using a suitable drying method, such as but not limited to a rotary evaporator, at a temperature of approximately 37° C. ($\pm 2^\circ$ C.). Other suitable drying methodologies include, but are not limited to, tray drying and spray drying.

[0053] In a specific embodiment, the directly compressible proanthocyanidin polymer composition is isolated as described in Section 10, *infra*.

bovine animals, swine, ovine animals, poultry (such as chickens), and equine animals, and other domesticated animals such as canine animals and feline animals. In particular the pharmaceutical formulations of the invention can be used to treat diarrheal disease in non-human animals, particularly food animals such as cattle, sheep and swine, caused by bacterial pathogens such as enterotoxigenic, enterohemorrhagic and other *E. coli*, *Salmonella* spp., *Clostridium perfringens*, *Bacteriodes fragilis*, *Campylobacter* spp., and *Yersinia enterocolitica*, protozoal pathogens, particularly *Cryptosporidium parvum*, and viral agents, particularly rotaviruses and coronaviruses, but also togavirus, parvovirus, calicivirus, adenoviruses, bredaviruses, and astroviruses.

[0086] Additionally, the pharmaceutical formulations of the invention may also be administered prophylactically to humans and non-human animals to prevent the development of secretory diarrhea. By way of example, but not by way of limitation, a proanthocyanidin polymer composition pharmaceutical formulation can be administered to tourists traveling to a country where there is a risk of travelers diarrhea at a time or times that are effective for preventing the disease. The pharmaceutical compositions of the invention can be administered to AIDS patients to prevent the occurrence of HIV-Associated Chronic Diarrhea. Also, the pharmaceutical compositions of the invention can be administered to children in a community threatened with cholera epidemic or rotavirus epidemic to prevent the spread of the disease. Likewise, the pharmaceutical compositions of the invention can be administered to farm animals, particularly young or recently weaned farm animals, to prevent the development of diarrheal disease.

[0087] When used according to the formulations and methods of the present invention as a treatment for secretory diarrhea, effective dosage ranges of the pharmaceutical formulations of the proanthocyanidin polymer composition for oral administration are in the range of 0.1 to 100 mg/kg per day, preferably about 0.1 to about 40 mg/kg per day, optionally 0.1 to 25 mg/kg per day, and also optionally 0.1 to 10 mg/kg per day. It should be appreciated that the appropriate dose will depend upon the type and severity of the secretory diarrhea. It has been found that human subjects can tolerate at least up to 2 grams of the proanthocyanidin polymer composition per day (25-30 mg/kg/day) for up to 2 days. It is believed that doses may exceed 40 mg/kg per day, optionally up to 100 mg/kg per day, if such dosages are necessary to treat the secretory diarrhea.

[0088] When used according to the formulations and methods of the present invention as a prophylaxis for secretory diarrhea, effective dosage ranges of the pharmaceutical formulations of the proanthocyanidin polymer composition for oral administration are in the range of 0.1 to 100 mg/kg per day, preferably about 0.1 to about 40 mg/kg per day, optionally 0.1 to 25 mg/kg per day, and also optionally 0.1 to 10 mg/kg per day. It should be appreciated that the appropriate dose will depend upon the type and severity of the secretory diarrhea to be prevented. It has been found that human subjects can tolerate at least up to 2 grams of the proanthocyanidin polymer composition per day (25-30 mg/kg/day) for up to 2 days. It is believed that doses may exceed 40 mg/kg per day, optionally up to 100 mg/kg per day, if such dosages are necessary to prevent the secretory diarrhea.

[0089] The proanthocyanidin polymer composition can be administered for treatment or prevention of secretory diarrhea in any therapeutically acceptable pharmaceutical form. The pharmaceutical composition can be administered orally, in the form of, such as but not limited to, drug crystals, granules, small particles (which include particles sized on the order of micrometers, such as microspheres and microcapsules), particles (which include particles sized on the order of millimeters) beads, microbeads, pellets, pills, microtablets, compressed tablets or tablet triturates, molded tablets or tablet triturates, and in capsules, which are either hard or soft and contain the composition as a powder, particle, bead, solution or suspension. The pharmaceutical composition can also be administered orally, as a solution or suspension in an aqueous liquid, as a liquid incorporated into a gel capsule or as any other convenient formulation for administration, or rectally, as a suppository, enema or other convenient form.

[0090] In a preferred embodiment, an enteric coated pharmaceutical composition containing the proanthocyanidin polymer composition is administered for the treatment or prevention of secretory diarrhea. In a more preferred embodiment, the enteric coated pharmaceutical composition is enteric coated tablets or beads of a directly compressible pharmaceutical composition, optionally containing a lubricant such as, but not limited to, magnesium stearate. Preferred enteric coated formulations include, enteric coated beads in a hard-shell gelatin capsule, enteric coated microspheres in a hard-shell gelatin capsule, enteric coated microspheres provided in a suspension or mixed with food, which preparations are particularly convenient for pediatric administration, and enteric coated compressed tablets. In another embodiment, a pharmaceutical composition containing the proanthocyanidin polymer composition and a compound which neutralizes stomach acid or inhibits the secretion of stomach acid is administered for the treatment of secretory diarrhea. In yet another embodiment, a pharmaceutical composition containing the proanthocyanidin polymer composition is administered either concurrent with or subsequent to administration of a pharmaceutical composition which either neutralizes stomach acid or inhibits the secretion of stomach acid for treatment of secretory diarrhea. The proanthocyanidin polymer composition can also be formulated as a suppository for rectal administration.

[0091] The pharmaceutical formulations of the invention can also be administered either alone or in combination with other agents for treatment or amelioration of secretory diarrhea symptoms such as rehydration agents, antibiotics, anti-motility agents, and fluid adsorbents, such as attapulgit.

[0092] The pharmaceutical formulations of the invention can also be incorporated into animal feed for use in treating secretory diarrhea in animals such as bovine animals, swine, ovine animals, poultry, equine animals, canine animals, and feline animals.

[0093] The following series of Examples are presented for purposes of illustration and not by way of limitation on the scope of the invention.

Jan. 27, 2005

by gently stirring the "EUDRAGIT™ L 30D-55" suspension continually and, in a separate container, suspending and homogenizing the triethyl citrate and talc in purified water. The triethyl citrate/talc mixture was then added to the "EUDRAGIT™ L 30D-55" suspension, and the resulting coating dispersion stirred during the spraying process to avoid settling. The beads were then coated in the fluidized bed processor under the following parameters: The inlet temperature was 42° C. to 47° C.; the outlet temperature was 28° C. to 34° C.; the air volume was 30-40 CMH; the spray rate was 6-12 grams/minute; and the air pressure was 2.5 Bars. The resulting enteric coated beads were then filled into a size #0 hard shell gelatin capsule.

8.3. Enteric Coated Granules and Power Particles

[0139] Described below is a method for formulating the proanthocyanidin polymer composition as enteric coated granules or powder (microspheres with a diameter of 300-500 μ) in either hard shell gelatin capsules or suspended in an oral solution. The proanthocyanidin polymer composition powder particles are prepared by high-shear powder mixing of the proanthocyanidin polymer composition and hydroxypropylmethylcellulose in a high speed mixer/granulator. The proanthocyanidin polymer composition granules are prepared by spraying polyvinylpyrrolidone on the powder in the high speed mixer/granulator so that the powder particles agglomerate to form larger granules. Using fluidized bed equipment, the granules or powder are then covered with a seal coat of Opadry Clear (mixed with water) and then coated with the enteric coating "EUDRAGIT™ L 30D" applied as an aqueous dispersion containing 30% w/w dry methacrylate polymer substance, which is supplied with 0.7% sodium lauryl sulfate NF (SLS) and 2.3% polysorbate 80 NF (Tween 20) as emulsifiers, to which the plasticizers, triethyl citrate and glyceryl monostearate, are added to improve the elasticity of the coating. The final composition of the enteric coated powder is 81.8% w/w proanthocyanidin polymer composition, 1.5% w/w hydroxypropylmethylcellulose, 0.5% w/w Opadry clear, 14.5% w/w "EUDRAGIT™ L 30D", 1.45% w/w triethyl citrate, and 0.25% w/w glyceryl monostearate. The final composition of the enteric coated granules is 81.8% w/w proanthocyanidin polymer composition, 10% polyvinylpyrrolidone, 1.5% w/w hydroxypropylmethylcellulose, 0.5% w/w Opadry clear, 14.5% w/w "EUDRAGIT™ L 30D", 1.45% w/w triethyl citrate, and 0.25% w/w glyceryl monostearate.

[0140] The enteric coated proanthocyanidin polymer composition granules or particles may be filled into a hard shell gelatin capsule in an amount which provides a suitable dosage.

[0141] The enteric coated proanthocyanidin polymer composition granules or powder particles can also be suspended in a solution for oral administration, particularly for pediatric administration. The suspension solution is prepared by wetting 2 grams hydroxypropylmethylcellulose in 97.8 ml distilled water and 0.2 grams Tween 80; mixing this preparation to homogeneity by sonicating, heating the solution to 40° C. and stirring for three hours; and then adding the enteric coated proanthocyanidin polymer composition powder particles or granules to the homogeneous solution.

8.4. Enteric Coated Compressed Tablets

[0142] A method for formulating the proanthocyanidin polymer composition with a diluent as enteric coated tablets

is described below. For each 350 mg tablet, 250 mg proanthocyanidin polymer composition is granulated with 7 mg crosslinked sodium carboxymethylcellulose ("AC-DI-SOL™") and a sufficient mass of microcrystalline cellulose ("AVICEL™ PH 200/300") to bring the total mass to 350 mg. These ingredients are mixed for 20 to 30 minutes in a V blender. After the 20 to 30 minutes of mixing, 1.75 mg magnesium stearate is added and the mixture is blended for an additional 4 to 5 minutes. The resulting granules are compressed on a rotary tablet press using 1/16th inch standard concave punches. The tablets are coated with an enteric coating mixture prepared from 250 grams "EUDRAGIT™ L 30D-55", 7.5 grams triethyl citrate, 37.5 grams talc and 205 grams water. The tablets are then placed in a perforated pan coater (e.g. the "ACCELA-COTA™" system) and rotated at 15 rpm at 40° C. The enteric coating formulation is sprayed using the following conditions: inlet air temperature of 44° C.-48° C., exhaust air temperature of 29° C.-32° C., product temperature of 26° C.-30° C., a 1 mm spray nozzle, a pan speed of 30 to 32 rpm, an airflow of 30-32 CFM, and a spray pressure of 20 PSI. The tablets are finally cured for 30 minutes as the pan is rotating at 15 rpm with an inlet air temperature of 60° C. and then, after shutting off the heat, the tablets are rotated at 15 rpm until the tablets have cooled to room temperature.

8.5. Enteric Coated Directly Compressed Tablets

[0143] A method for formulating the proanthocyanidin polymer composition without a diluent as enteric coated tablets was carried out as described below. Directly compressible proanthocyanidin polymer composition was produced according to the method described in Section 10, infra. 125 mg tablets were prepared by blending 99.6% w/w directly compressible proanthocyanidin polymer composition with 0.40% w/w magnesium stearate for two minutes and then directly compressing the material into 125 mg tablets on a rotary press using 1/4 inch diameter round standard concave punches to a tablet hardness of 4-10 Kp.

[0144] The core tablets were tested and found to have an average hardness (n=10) of 4-10 Kp, friability (n=20) of less than 0.7%, an average table weight (n=10) of 125 mg $\pm$ 7 mg, an average thickness (n=10) of 3.9 to 4.1 mm, and a disintegration time (n=6) of not more than 20 minutes.

[0145] The coating dispersion was prepared by mixing, per 100 grams of tablets, 22.22 grams of a 30% w/w "EUDRAGIT™ L 30D-55" suspension, kept gently stirred with a mixture of 0.67 grams triethyl citrate, 1.67 grams talc and 20.44 grams purified water which had been mixed until homogeneous. The coating dispersion was continually stirred to avoid settling.

[0146] The tablets (in batches of 100,000) were coated with the coating dispersion in a Compu-Lab 24 inch/30 L pan. The tablets were jogged in the pan at a speed of 3-5 rpm and pre-warmed to a temperature of 35° C. to 40° C. The tablets were then coated with the enteric coating dispersion to a 6% to 8% weight gain with the following parameters: an inlet temperature of 45° C. to 65° C.; an exhaust air temperature of 27° C. to 34° C.; a product temperature of 28° C. to 32° C.; a pan speed of 8-14 rpm; an air flow of 180 to 240 CHM; an air spray pressure of 10-20 psi (pounds per square inch); an initial spray rate of 3 to 4 grams/min/kg; and a final spray rate of 4 to 8 grams/min/kg. The tablets were

then cured for 30 minutes in the pan with an inlet temperature of 45° C. to 50° C. and a pan speed of 3 to 5 rpm. Finally, the tablets were allowed to cool to room temperature in the pan at a pan speed of 3 to 5 rpm. Four of the 125 mg tablets were then filled into a size zero, opaque Swedish orange-colored gelatin capsule.

[0147] The enteric coated proanthocyanidin polymer composition tablets were tested for content uniformity, drug release, microbiological tests and stability, and some analytical in process tests were also performed. In stability studies, the proanthocyanidin polymer composition remained stable after six months of storage at room temperature as well as under accelerated temperature and humidity conditions. Finally, the core tablets were tested and found to have an average hardness (n=10) of 4-10 Kp, friability (n=20) of less than 0.7%, an average tablet weight (n=10) of 125 mg±7 mg, an average thickness (n=10) of 3.9 to 4.1 mm, and a disintegration time (n=6) of not more than 20 minutes.

8.6. Enteric Coated Directly Compressed Tablets

[0148] Formulation of the proanthocyanidin polymer composition, without a diluent, as enteric coated tablets was carried out as described below. The directly compressible proanthocyanidin polymer composition was isolated as described in Section 10, *infra*. The core tablets were prepared by milling 250 mg proanthocyanidin polymer composition per tablet (approximately 16 kg total) in a Quadro Comil with an 024R (30 mesh) screen and then blending the milled composition in a Patterson Kelley 2 cubic foot twin shell blender. 1 mg magnesium stearate (Spectrum Quality Products, Inc., New Brunswick, N.J.) per tablet was then added to the composition in the blender and blended for 2 minutes. The blend was then compressed into 251 mg tablets (containing 250 mg proanthocyanidin polymer composition) on a rotary tablet press to a tablet hardness of 8-15 Kp and friability less than 0.5%.

[0149] The coating dispersion was prepared by first mixing in a first container the 25 g (7.5 g solids) "EUDRAGIT™ L 30 D-55" (Huls America, Inc., Somerset, N.J.) (weight given per 115 grams coated tablets) dispersion. The pigment dispersion was prepared by adding sequentially with constant stirring in a second container 39.59 g purified water, 3.30 grams talc (Alphafil™ 500) (Whittaker, Clark & Daniels, Inc., South Plainfield, N.J.), 6.06 g (3.15 g solids) White Dispersion (pigment) (Warner-Jenkinson, Inc., St. Louis, Mo.), and then 1.05 g triethyl citrate (Morflex, Inc., Greensboro, N.C.). The mixture was then homogenized for 15 minutes or until homogenous. While slowly stirring, the pigment dispersion was added to the "EUDRAGIT™ L 30 D-55" dispersion and then stirred for 30 minutes before spraying. Stirring was also maintained during the spraying process to avoid settling.

[0150] The tablets were coated in batches of 50,000 in a Compu-Lab 24 inch/30 L pan with the following settings: 10-20 psi atomizing air pressure; 35° C.-60° C. pan inlet air temperature; 5 to 6 inches nozzle tip to tablet bed distance; and 4/2 baffles/nozzles. After adding the tablets to the pan, the pan was jogged at a speed of 3 to 5 rpm and heated to 40° C. The tablets were then sprayed to a weight gain of 11 to 13% with the following parameters: 27°-33° C. target exhaust temperature (to be achieved within ten minutes of

spraying); pan speed of 8 to 12 rpm; 180-240 CFM air flow; and a spray rate of 2-5 g/min/kg. After achieving the desired weight gain, the heat was shut off and the pan jogged at 3-5 rpm until the tablets were cooled to below 30° C.

[0151] The tablets were encapsulated in size AA opaque Swedish orange colored DB gelatin capsules (Capsugel, Greenwood, S.C.).

[0152] 500 mg tablets were also produced as described above, except that coating was done on batches of 25,000 tablets to a weight gain of 8 to 10%.

8.7. Suppositories

[0153] Formulation of the proanthocyanidin polymer composition as a suppository for rectal administration is described below. One suppository formulation for the proanthocyanidin polymer composition can be prepared by heating 91 grams glycerin to 120° C., dissolving 9 grams sodium stearate in the heated glycerin, then adding 5 grams purified water. 5% to 50% proanthocyanidin polymer composition is added to the base and the mixture is then poured into a suitable mold. Alternatively, the suppository may be prepared by heating 20 grams gelatin and 70 grams glycerin to 70° C. and stirring for 2 hours, then adding 10 grams proanthocyanidin polymer composition which has been dissolved in purified water by sonicating for 5 minutes, and stirring at 40° C. until a homogeneous mixture is achieved. The preparation may then be poured into a mold suitable for preparing suppositories.

9. EXAMPLE

Effect of the Proanthocyanidin Polymer Composition Formulations in Patients Suffering from Traveler's or Non-Specific Diarrhea

[0154] Summarized below are interim results obtained from the initial 20 patients of an open-label clinical trial of safety and effectiveness of the proanthocyanidin polymer composition from *C. lechleri* for the symptomatic treatment of acute non-specific diarrhea and traveler's diarrhea.

9.1. Human Safety and Efficacy Study

[0155] A total of 20 patients with traveler's diarrhea were entered into the study. The patient population consisted of young (average age=24 years) male and female patients who were students from the United States in Mexico. The students were recruited by the investigator as they entered the country and were told to report to the clinic after developing diarrhea and before starting any other medications.

[0156] Subjects were evaluated for the following parameters:

[0157] a) Usual stool frequency (number of stools per day or week).

[0158] b) Date and time of diarrhea onset.

[0159] c) Number of stools in the past 24 hours, categorized according to consistency as follows:

[0160] Formed: retains its original shape in water

[0161] Soft: assumes shape of the container

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16



US008709515B1

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Colitz et al.

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(54) **NUTRITIONAL SUPPLEMENT METHOD**

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None

See application file for complete search history.

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(57) **ABSTRACT**

The method comprises steps of: providing a nutraceutical including, in combination, 1.13 to 3 mg lutein and 18.8 to 51.2 mg omega fatty acids and 1.9 to 5.2 mg grape seed extract and 1.9 to 5.2 mg alpha lipoic acid; determining the weight of each dose of the components in the combination based upon an amount per kg body weight of the animal patients; and administering 1 dose of nutraceutical per day to animals suffering from ocular health issues including any degenerative retinal disease and diabetic cataracts and prior to and following cataract surgery for the diminishment and prevention of secondary cataracts.

3 Claims, No Drawings

NUTRITIONAL SUPPLEMENT METHOD

RELATED APPLICATION

The present application is a continuation-in-part of pending application Ser. No. 12/378,738 filed Feb. 19, 2009, the subject matter of which is incorporated herein by reference.

FIELD OF INVENTION

The invention is directed to maintain ocular health, slow the progression of inherited and age related retinal degeneration, possibly slow or halt the death of photoreceptors in Sudden Acquired Retinal Degeneration Syndrome, SARDS; provide mild anti-inflammatory benefits (lutein, GSE, others); possibly slow or prevent the cataractous changes due to retinal degeneration and senile changes and chronic sunlight exposure; and possibly benefit diabetic patients as many components help to stabilize glucose use and metabolism. The invention has been shown to significantly slow the onset of diabetic cataracts. A research project is presently ongoing.

BACKGROUND OF THE INVENTION

The Lens—The crystallin lens is a transparent biconvex, M&M shaped, structure located behind the iris of the eye. The basic anatomy of the lens includes an outer lining, lens capsule, surrounding the lens material. The lens material has two major subdivisions, the nucleus, which is the innermost aspect, and the surrounding layers, called the cortex. The anterior aspect of the lens capsule is lined with a single layer of cells called the lens epithelial cells. There are three distinct subgroups of these cells: the central region has cells that are very slow to proliferate unless they undergo trauma, such as cataract surgery, the germinative region has cells that are proliferative and their progeny migrate laterally to the equatorial region. The cells in the equatorial region develop into elongated fiber cells that span from the anterior aspect to the posterior aspect of the lens, with the newer cells overlying the older cells in an organized pattern, similar to rings in a tree trunk. The lens' function, along with the cornea, is to focus light onto the retina for sight. In humans, non-human primates, and some other species the lens can change shape in order to continually focus on objects located at different distances. This change in shape is called accommodation and is strongest in youth, but becomes more difficult with normal aging as the lens becomes more densely packed with cells.

The internal portion of the eye has two fluid-containing chambers: the anterior segment contains the aqueous humor or aqueous, and the posterior segment contains the vitreous humor or vitreous. Both of these fluids bathe the lens and provide nutrients and take away waste material.

Cataracts—A cataract is any opacity of the lens capsule or its cortex or nucleus or any combination of these and can affect all species of animals. Causes of cataracts are numerous and include excessive exposure to oxidative stressors, including ultraviolet irradiation or sunlight, as well as other forms of radiation, genetics, diabetes mellitus, nutritional imbalance, toxins, and normal aging changes, among others. Thus far, there is no medical way in which to treat an existing cataract, only surgery to remove the cataract will address the problem. The incidence of cataracts in the general animal and human population depends on the definition. If defined as just any opacity that affects the lens or its capsule, then the incidence is likely very high. However, if this opacity significantly impacts vision, then the incidence may only affect less than five percent of all animals. This percentage increases

with age in all species. It is estimated that 10,000 to 12,000 cataract surgeries are performed annually in dogs; this makes it one of the most common surgical procedures performed in this species. Cataract surgery is also the most common surgery performed in humans.

There are species differences in terms of causes of cataracts. The leading cause of cataracts in humans is exposure to sunlight; other causes include diabetes mellitus and inheritance. Common causes of cataracts in dogs are inheritance, breed-predisposition, and diabetes mellitus. Cats develop visually impairing cataracts due to chronic uveitis as do horses; though both species can uncommonly develop inherited or nutritional cataracts.

Retina—Retinal Degeneration aka Progressive Retinal Atrophy is another inherited disease that affects dogs more commonly than cats or other species. Numerous pure breed dogs and a few pure breed cats have been shown to be genetically predisposed to this problem. The disease is typically diagnosed by ophthalmoscopy when the dogs are young adults, under 6 years of age; though some forms of the disease can begin earlier. However, the disease can be diagnosed in most forms before 1.5 years of age by electroretinography. The majority of inherited retinal degenerations affect the rods first, then eventually the cones; very few affect the cones first.

Sudden Acquired Retinal Degeneration Syndrome (SARDS) is another type of retinal degeneration with an unknown cause that affects the rods and cones acutely. It typically affects middle-aged spayed female dogs, though any breed or sex can be affected. Dogs present with a sudden loss of vision over a few days to 1-2 weeks. The pupils usually respond to light incompletely until late in the disease. Early, there are negligible fundic changes, however, with time, the arterioles attenuate more rapidly than the venules. Histologically, the rods and cones die by apoptosis, which explains the electroretinographic results ie flat with no wave form. Over time, the rest of the retinal layers degenerate. To date, there is no way to cure this disease once vision is completely lost.

Dietary Supplements are commonly used for the prevention of chronic disease, improved overall health, and in some cases to treat or address some medical conditions. Their use for specific ocular conditions has been advocated in the literature; these include retinal or macular degeneration, cataracts, dry eye and others.

Recent literature suggests that glucose, fatty acids, amino acids, vitamins, minerals, supplements, other nutrients or their respective metabolites regulate gene expression in a hormone-independent manner. In fact, bioactive food components, including vitamins, minerals, carotenoids, flavonoids, monoterpenes and phenolic acids are now thought to act as transcriptional modulators directly affecting gene expression. Obesity is a risk factor for cataract formation in humans. Therefore, perhaps improving the overall health status of the human or animal but supplementing with antioxidants may modulate genes that predispose that human or animal to genetic or environmentally induced diseases.

Carotenoids—Epidemiological and interventional studies suggest that increased consumption of foods rich in antioxidants such as vitamin C, vitamin E and selective carotenoids protect the human and primate lens against UVR-induced oxidative stress and thereby decrease the risk of developing cataracts. Recent attention has focused on the possible roles of lutein, LUT; and zeaxanthin, ZEA, in ocular health. These oxycarotenoids, oxygenated carotenoids or xanthophylls, selectively accumulate in the lens and the macular region of the human and primate accumulate in the lens by unknown mechanisms. There are also trace levels of lutein and zeaxanthin in the cornea and sclera, the lens and uveal structures

have higher levels. The macula has 33 ng and the peripheral retina has 65 ng of these carotenoids. It has been proposed that these compounds may be particularly effective in preventing cataracts and age-related macular degeneration. Indeed, increased plasma and/or dietary levels of these carotenoids are associated with significantly decreased risk of developing cataracts and macular degeneration. Conversely, experimental animals, e.g., primates, fed diets lacking LUT and ZEA are significantly more susceptible to developing cataracts. One human study found that lutein and zeaxanthin appears beneficial for age-related macular degeneration and cataract formation. Such observations have resulted in the appearance of numerous lutein supplements in the human health marketplace. For example, Centrum multi-vitamin and mineral pills now include lutein and the label indicates that this carotenoid "helps maintain healthy eyes".

The importance of dietary LUT and ZEA in canine vision and cataractogenesis is unknown. Kim et al. recently reported that LUT was not detectable in the plasma of 18 month old beagles fed a standard canine diet. However, plasma LUT increased rapidly and immune function was enhanced in response to dietary supplementation with LUT. The possibility that LUT supplementation resulted in the accumulation of the xanthophylls in ocular tissues was not examined. Since supplementation of humans and primates with xanthophylls induced a gradual increase in retinal xanthophylls in humans and primates, 10, 11 it is feasible that LUT and ZEA will accumulate in canine ocular tissues in response to supplementation.

Lycopene is another major carotenoid which is found primarily in tomatoes. Of all known carotenoids, lycopene has been shown to have the highest physical quenching rate constant with singlet oxygen species. Lycopene has been shown to protect against cataract formation in vitro and in vivo.

Omega Fatty Acids—Puppies fed diets with high fish oil supplementation had improved visual performance as evidenced by increased rod response using electroretinography. They also had shorter response times, improved response to dim light and increased activation of the neural cascade. Puppies fed either flaxseed oil or only ALA, alpha linoleic acid, the precursor to EPA and subsequently DHA, had lower or minimal improvements in these parameters. This is likely due to the slow and inefficient conversion of ALA to EPA, and then to DHA. Therefore, feeding preformed dietary n-3 long chain PUFAs, polyunsaturated fatty acids, is a more efficient way to enrich diets with DHA. A review of the human literature which evaluated the evidence for the effectiveness of omega-3 fatty acids in preventing the development or progression of retinitis pigmentosa, a disease analogous to Progressive Retinal Atrophy in dogs, found trends in improvement in some of the studies. The same group evaluated the literature for the effectiveness of omega-3 fatty acid in slowing the progression of age-related macular degeneration. Only one study was found, but it demonstrated the efficacy of omega-3 fatty acids in preventing AMD to its advanced form. Omega-3 fatty acids may protect the vascular and neural retina against inflammatory-, light-, ischemia-, oxygen-, and age-related pathology. Omega-3 fatty acids have also been shown to be beneficial for the prevention of cataract in humans.

Vitamin C, Ascorbic Acid—Vitamin C is a hydrophilic molecule that scavenges free radicals. It is the strongest physiological antioxidant that acts in the aqueous environment of the host. It is a very safe antioxidant, likely due to its water solubility, with no safe upper dose limit set by the Expert Group on Vitamins and Minerals of 2003. Vitamin C is found in the lens and in the aqueous humor of most species,

including dogs, cats, humans, and cattle. Its function relates to the oxidation-reduction reactions or is coupled to glutathione metabolism. One ten year study found that vitamin C protects against nuclear cataract formation in humans. Numerous other studies found that supplementation with vitamin C and elevated blood levels of this antioxidant were associated with decreased incidence in at least one type of cataract. In humans, vitamin C concentrations decrease with age and more so in patients with senile cataract. A study in Cocker Spaniels found that those with cataracts had lower vitamin C levels than those without cataracts suggesting that there is a decrease in antioxidant capacity in the aqueous humor of dogs with cataracts. Whether this was a cause or an effect was not identified.

Vitamin E—Vitamin E is a fat soluble, lipophilic, antioxidant that interferes with the chain reaction of lipid peroxidation. Vitamin C works synergistically with vitamin E, i.e. vitamin E is oxidized to tocopheroxyl radical which is reduced back to tocopherol by vitamin C. Numerous studies have strongly suggested that consistent intake of vitamin E and high plasma vitamin E levels had a lower prevalence of various types of cataracts in humans. Higher blood levels of vitamin E are also protective against age-related macular degeneration in humans. Vitamin E is the major antioxidant present in cell membranes; it is highly concentrated in rod photoreceptor outer segments and the retinal pigment epithelium. It may also protect vitamin A from oxidative degeneration the retina.

Proanthocyanidins—Proanthocyanidins are naturally occurring compounds found at high concentrations in fruits, vegetables, wine, tea, nuts, seeds, flowers, bark and cacao. Proanthocyanidins have a wide range of biological activities such as antioxidant and free radical scavenging capabilities, anti-inflammatory and antimicrobial properties, inhibition of cancer cell growth, prevention of low density lipoproteins oxidation, cardioprotection, and inhibition of viral replication. In vitro experiments utilizing grape seed proanthocyanidin extract, GSE, have shown GSE to be a more potent free radical scavenger than vitamin C or vitamin E. Furthermore, GSE has been shown to prevent cataract formation in a hereditary cataractous rat model and in a diabetic rat model. GSE may have use as a dietary supplement to prevent and/or delay cataract formation. GSE significantly decreases TBHP-induced intracellular ROS production and oxidant-induced cell signaling pathways associated with cataractogenesis, as well as UV-induced changes associated with cataractogenesis. It also lowers blood glucose levels in diabetics and improves endothelial cell function.

Zinc—Zinc is an essential trace element essential for numerous homeostatic functions. It is an antioxidant that offers protection against some, but not all, ROS mediated injury. It competitively displaces iron from binding sites on negatively charged phospholipids and prevents its redox cycling. When combined with vitamin E it has synergistic protection against Fe-mediated lipid peroxidation. It is also important to the health of the retina and in the function of vitamin A. Zinc deficiency reduces plasma levels of retinol-binding protein and retinol reductase with a subsequent decrease in vitamin A in the retina. One human study showed it to slow the progression of macular degeneration. Zinc is also important in protecting the lens from cataractogenesis by its antioxidant effects. Zinc deficiency in some species has been associated with increased risk of cataract formation.

Epigallocatechin gallate, EGCG—Both green and black teas significantly inhibit diabetic cataracts by reducing certain biochemical indicators as well as glucose. Another study showed similar results but also suggested an increase in insu-

lin activity. Retard the progression of cataract in selenite induced cataracts in rats. A recent study found that EGCG fed in the water to albino rats attenuated light-induced photoreceptor damage. In addition, EGCG given to rats wherein one eye had an induced increase in intraocular pressure attenuated retinal neuronal death. This supports EGCG's neuroprotective capabilities and may be beneficial in cases of glaucoma.

Alpha Lipoic Acid—Alpha lipoic acid is an antioxidant that potentiates vitamin C and vitamin E levels; it also has anti-inflammatory effects. It has traditionally been used for diabetic neuropathy and in ischemia-reperfusion injury. It was included in this recipe primarily for the numerous diabetic canine patients seen in veterinary practice. It is not in the feline formula as it may not be safe in cats at a dose higher than 30 mg/day.

Alpha lipoic acid is an antioxidant that potentiates Vitamin C and Vitamin E levels. Alpha lipoic acid has anti-inflammatory effects. Alpha lipoic acid has traditionally been used in humans for diabetic neuropathy and in ischemia-reperfusion injury. (Mandelker and Wynn, 2004) Alpha lipoic acid's primary function is to increase the body's production of glutathione, an important antioxidant mechanism in the crystallin lens, that may protect against cataract. One study found that alpha lipoic acid protects the lens from oxidative stress. (Maitra et al., 1995) Alpha lipoic acid is included in Ocu-GLO Rx™ primarily to benefit diabetic canine patients as it promotes normal insulin sensitivity and glucose metabolism. (Jacob et al., 1995, Nichols, 1997) By helping to balance insulin/glucose metabolism, secondary cataract due to hyperglycemia may be slowed or prevented.

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MAITRA, I., SERBINOVA, B., TRISCHLER, H. & PACKER, L. (1995) Alpha-lipoic acid prevents buthionine sulfoximine-induced cataract formation in newborn rats. *Free Radic Biol Med*, 18, 823-829.

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B vitamin mix—The B vitamins function in a variety of essential processes and were included in this recipe for the overall health of the body. Vitamin B1, thiamine, is important in neuromuscular development and maintenance as well as carbohydrate and fat utilization for energy production and cellular metabolism. Vitamin B3, niacin, is likewise involved in energy production but also in fat and steroid synthesis and lowers total levels of serum cholesterol, low density lipoproteins, very low density lipoproteins, and triglycerides. Vitamin B5, pantothenic acid, is essential for breakdown of fatty acids, steroids, cholesterol and amino acids and functions as an antioxidant. It is incorporated into coenzyme A, which is important in oxidative phosphorylation. Vitamin B6, pyridoxine, is essential for hemoglobin formation and important for utilization for stored glucose. It is essential in the metabolism of fats, proteins, and carbohydrates. Vitamin B12, cyanocobalamin, is an enzyme cofactor essential for normal cell growth and red blood cell development. Folic acid, aka vitamin B9, is essential for cell growth and development and for preventing neural tube defects in developing fetuses. It has anticarcinogenic abilities in elderly humans and insufficient intake may result in anemia. Biotin, aka Vitamin H, is an

enzyme cofactor involved in biosynthesis of fats and carbohydrates and metabolism of amino acids. Biotin has been shown to improve glucose tolerance and decrease insulin resistance.

Co-Enzyme Q10—Co-enzyme Q10, aka ubiquinol, is a lipid-soluble antioxidant that can be synthesized de novo and regenerated through a specific enzyme system in animal cells. It is not regarded as a vitamin because it is synthesized by all animal tissues. It functions to protect against lipid peroxidation and, therefore, functions as an antioxidant. Ubiquinol mediates electron transport in the mitochondrial respiratory chain, it supports energy metabolism and is a catalyst in ATP production.

SUMMARY OF THE INVENTION

The present invention refers to the use of supplementing an animal or human in effective amounts of a combination of antioxidants for the inhibition or progression of any retinal degeneration, for the prevention or slowing of the progression of cataract formation, for the improvement of dry eye disease, and for the overall enhanced health of the eye. By combining these antioxidants in amounts that are effective and in such a combination that various antioxidant pathways are addressed, this will optimize the ocular health of normal individuals and enhance conditions that are exacerbated or caused by oxidative stress.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention refers to the use of supplementing an animal or human in effective amounts of a combination of antioxidants for the inhibition or progression of any retinal degeneration, for the prevention or slowing of the progression of cataract formation, for the improvement of dry eye disease, and for the overall enhanced health of the eye. By combining these antioxidants in amounts that are effective and in such a combination that various antioxidant pathways are addressed, this will optimize the ocular health of normal individuals and enhance conditions that are exacerbated or caused by oxidative stress.

The supplement may be any suitable form of a pill, capsule preferably but not limited to a soft chewable gelatin capsule, tablet, chewable treat, liquid, slurry, or any other ingestible form, containing the previously mentioned ingredients in the effective ranges to be specified here. Not only is the specific combination of synergistic ingredients essential to the effectiveness of said invention, but the proper dosing as well. It is believed that sub-therapeutic levels are currently being proposed and commercially provided, contrary to successful studies showing a need for higher dosage levels. It is vital and unique to this invention that proposed ingredients be present in sufficiently high concentrations and purity, a minimum of 90 percent purity must be maintained, but preferably 95-99.9 percent purity for all ingredients, in order to maximize the potential for halting or delay of the previously discussed ocular diseases.

Example 1

Production of a chewable, flavored soft gelatin capsule is accomplished by filling soft gelatin capsules with the active ingredients which have been combined into a thick oil suspension, or slurry, and flavored with a suitable flavoring agent. The capsules are filled under specific laboratory conditions, utilizing liquid nitrogen to displace any air from

remaining inside the filled capsules. The capsule is then sealed and allowed to dry. A powdered flavoring may be dusted over the finished capsule, or a light spraying of a misted form of the flavoring may be passed over the product, to enhance appeal and compliance of the product. The process of filling the capsules under liquid nitrogen controlled conditions limits, or eliminates, air from being trapped inside the capsule, therefore limiting, or nearly eliminating, the oxidation process known to destroy anti-oxidants.

Example 2

Production of a soft chewable flavored dosage form, or treat, is accomplished by combining active ingredients with inert fillers such as but not limited to soy protein, flour, xanthan gum, and silica, with flavorings of sugar, appropriate levels of liquid flavorings, and commercial dog food added to increase palatability. The product is then pressed into 5 gram chewable doses and allowed to dry.

Example 3

An opaque gelatin capsule may be filled with 1 ml active ingredients, omitting the flavoring agents. Capsules are then tightly sealed and provided as an oral dosage. Note: Example 1 is the preferable system for capsules, even in the absence of flavoring inside or out, as the integrity of the product produced under the liquid nitrogen process is preferable.

Ingredient	Amount per kg body weight, based on 1 gelscap per day
Lutein and zeaxanthin	1.13 to 3 mg
Omega fatty acids	18.8 to 51.2 mg
Vitamin C	7.5 to 20.8 mg
Vitamin E	3.75 to 10.4 mg
GSE	1.9 to 5.2 mg
zinc	0.38 to 1.04 mg
Lycopene	0.1 to 0.3 mg
EGCG	1.13 to 3.125 mg
alpha lipoic acid	1.9 to 5.2 mg
B1, thiamine	0.0075 to 0.02 mg
B3, niacin	0.09 to 0.25 mg
B5, pantothenic acid	0.075 to 0.2
B6, pyridoxine HCl	0.0075 to 0.02 mg
B12, cyanocobalamin	0.0002 to 0.0005 mg
Folic acid	0.0015 to 0.004 mg
Biotin	0.00075 to 0.048 mg
Co Q10	1.9 to 5.2 mg
Silymarin	7 to 15 mg

The present invention is a combination of nutritional supplements that may enhance overall ocular health, specifically slow/prevent retinal degenerative diseases and cataracts.

The polyphenol, grapeseed extract, free radical scavenger chelation of transition metals, protects against lipid peroxidation of LDL cholesterol; inhibits against DNA fragmentation, apoptosis; protects retinal microvasculature possibly by increasing the rate of rhodopsin regeneration; has a Vitamin E sparing effect; inhibits formation of proinflammatory cytokines IL1 β and TNF. It may also lower blood glucose levels in diabetic patients and improve endothelial cell function.

The carotenoid pigments including lutein and zeaxanthin act as antioxidants and protect cell membranes by stabilizing the oxygen radicals produced when phagocytic granulocytes undergo respiratory bursts that destroy intracellular pathogens.

The carotenoid, lycopene, prevents free radical damage by reactive oxygen species; modulates intercellular gap junction communication; and may protect against hyperglycemia.

The omega fatty acids are potent antioxidants that slow the progression or prevent the onset of various forms of retinal degeneration.

The carotenoid, lycopene, prevents free radical damage by reactive oxygen species; modulates intercellular gap junction communication; and may protect against hyperglycemia.

Vitamin C, ascorbic acid, is normally present in the aqueous humor and lens of most species and elevated levels protect against some types of cataract.

Vitamin E, alone or mixed tocopherols and tocotrienols, inhibits COX2 activity; is the major antioxidant present in cell membranes; and is concentrated in rod photoreceptor outer segments and the retinal pigment epithelium. It may also protect vitamin A from oxidative degeneration in the retina. Therefore, it may protect against various forms of retinal degeneration.

The polyphenol, grapeseed extract, free radical scavenger chelation of transition metals, protects against lipid peroxidation of LDL cholesterol; inhibits against DNA fragmentation, apoptosis; protects retinal microvasculature possibly by increasing the rate of rhodopsin regeneration; has a Vitamin E sparing effect; inhibits formation of proinflammatory cytokines IL1 β and TNF. It may also lower blood glucose levels in diabetic patients and improve endothelial cell function.

Zinc offers protection against some, but not all, ROS mediated injury; competitively displaces iron from binding sites on negatively charged phospholipids; and prevents its redox cycling.

EGCG quenches reactive oxygen species, prevents oxidative cross-linking of test proteins, and inhibits single strand DNA breaks in whole cells. It also counteracts the oxidative insult from cigarette smoke and retards the progression of cataract in selenite induced cataracts in rats. It also inhibits diabetic cataracts in rat models by a hypoglycemic effect and also decreased triglycerides in the same rats.

The B vitamins function in a variety of essential processes and were included in this recipe for the overall health of the body including neuromuscular development and maintenance as well as carbohydrate and fat utilization—Vitamin B1, thiamine; energy production, fat and steroid synthesis and lowering of total levels of serum cholesterol, low density lipoproteins, very low density lipoproteins, and triglycerides—Vitamin B3, niacin; breakdown of fatty acids, steroids, cholesterol and amino acids and functions as an antioxidant—Vitamin B5, pantothenic acid; hemoglobin formation and utilization of stored glucose as well as metabolism of fats, proteins, and carbohydrates—Vitamin B6, pyridoxine; as an enzyme cofactor essential for normal cell growth and red blood cell development—Vitamin B12, cyanocobalamin; and biosynthesis of fats and carbohydrates and metabolism of amino acids as well as improved glucose tolerance and decreased insulin resistance.

Folic acid, i.e. vitamin B9, may have anticarcinogenic abilities in the elderly.

Alpha lipoic acid, an antioxidant, improves glucose transport in muscles following exercise and is used in the management of insulin resistance i.e. type II diabetes.

Biotin, i.e. Vitamin H, is an enzyme cofactor involved in biosynthesis of fats and carbohydrates and metabolism of amino acids. Biotin has been shown to improve glucose tolerance and decrease insulin resistance which is important in the prevention and control of diabetes.

Co-enzyme Q10, an antioxidant, supports energy metabolism and is a catalyst of ATP production.

Milk thistle, also referred to as silymarin, silibinin, Silybum marianum, mariendistel, and Carduus marianus is a potent antioxidant with relevant effects against biological reactive oxygen species and lipid peroxidation. Silymarin also protects skin cells against ultraviolet radiation A induced damage including DNA strand breaks, lipid peroxidation and oxidative stress.

The present invention is a nutritional supplement system for enhancing the overall ocular health of animals by slowing and preventing degenerative diseases, cataracts and other maladies. The system comprises components in combination. In its broadest embodiment, the first component is provided is 1.13 to 3 mg lutein and zeaxanthin. The next component provided is 18.8 to 51.2 mg omega fatty acids. The last component provided is 1.9 to 5.2 mg grape seed extract. The weight of the components of the system are based upon an amount per kg body weight based on 1 dose per day.

An additional embodiment the system adds a nutritional supplement for abating heart disease. The supplement for abating heart disease is chosen from the class of heart disease abating supplements including 3.75 to 10.4 mg vitamin E and 1.9 to 5.2 mg Co Q10.

In another embodiment, the system adds an additional nutritional supplement for abating cataracts. The supplement for abating cataracts is chosen from the class of cataract abating supplements including 7.5 to 20.8 mg vitamin C and 0.1 to 0.3 mg lycopene.

In still another embodiment, the system adds an additional nutritional supplement for abating cancer. The supplement for abating cancer is chosen from the class of cancer abating supplements including 0.38 to 1.04 mg zinc, 1.13 to 3.125 mg EGCG, green tea, 0.0015 to 0.004 mg folic acid, and 7 to 15 mg silymarin.

In yet another embodiment, the system adds an additional nutritional supplement for abating diabetes. The supplement for abating diabetes is chosen from the class of diabetes abating supplements including 1.9 to 5.2 mg alpha lipoid acid and 0.00075 to 0.048 mg biotin.

In a final embodiment, the system adds an additional nutritional vitamin supplement for overall health enhancement. The supplement for overall health enhancement is chosen from the class of health enhancing vitamin supplements including 0.0075 to 0.02 mg B1, thiamine; 0.09 to 0.25 mg B3, niacin; 0.075 to 0.2 mg B5, pantothenic acid; 0.0075 to 0.02 mg B6, pyridoxine Hcl; and 0.0002 to 0.0005 mg B12, cyanocobalamin.

Lastly the present invention is a method for enhancing overall ocular health in animal patients. The method comprises a plurality of steps.

The first step is providing a nutraceutical. The nutraceutical includes, in combination, 1.13 to 3 mg lutein and 18.8 to 51.2 mg omega fatty acids and 1.9 to 5.2 mg grape seed extract and 1.9 to 5.2 mg alpha lipoic acid.

The next step is determining the weight of each dose of the components in the combination based upon an amount per kg body weight of the animal patients.

The last step is administering 1 dose of nutraceutical per day to animals suffering from ocular health issues including any degenerative retinal disease and diabetic cataracts. The administering being prior to and following cataract surgery for the diminishment and prevention of secondary cataracts.

It should be appreciated that the components of the present invention have primary benefits as set forth above. It should be further appreciated that such components also have an additional benefit and/or benefits, known or not known. Together, however, the components of the present invention entice ocular and additional benefits, particularly in animals.

As to the manner of usage and operation of the present invention, the same should be apparent from the above description. Accordingly, no further discussion relating to the manner of usage and operation will be provided.

With respect to the above description then, it is to be realized that the optimum dimensional relationships for the parts of the invention, to include variations in size, materials, shape, form, function and manner of operation, assembly and use, are deemed readily apparent and obvious to one skilled in the art, and all equivalent relationships to those illustrated in the drawings and described in the specification are intended to be encompassed by the present invention.

Therefore, the foregoing is considered as illustrative only of the principles of the invention. Further, since numerous modifications and changes will readily occur to those skilled in the art, it is not desired to limit the invention to the exact construction and operation shown and described, and accordingly, all suitable modifications and equivalents may be resorted to, falling within the scope of the invention.

What is claimed as being new and desired to be protected by Letters Patent of the United States is as follows:

1. A method for enhancing ocular health in a non-human subject comprising the steps of:

- (a) determining the body weight of the subject in kilograms;
- (b) administering 1 dose per day of a nutraceutical to the subject in need thereof, wherein the dose of the nutraceutical consists of 1.3 to 3 mg/kg BW lutein, 18.8 to 51.2 mg/kg BW omega fatty acids, 1.9 to 5.2 mg/kg BW grapeseed extract, and 1.9 to 5.2 mg/kg BW alpha lipoic acid.

2. The method of claim 1, wherein said subject suffers from a degenerative retinal disease or diabetic cataracts.

3. The method of claim 1, wherein said administering is performed prior to and following cataract surgery to diminish the development of secondary cataracts.

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