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Abogados

Apartado 3692

SUPERINDUSTRIA Y COMERCIO

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

(S.I.) 3002/00

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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

RESPUESTA A OFICIO 07230 DE SEPTIEMBRE 05, 2003

REF: Expediente No. 02 111.663 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/US01/14956

a favor de COLGATE – PALMOLIVE COMPANY

Titulada: COMPOSICIÓN ORAL SINERGÍSTICA ANTIPLACA-ANTIGINGIVITIS

RAMIRO CASTRO DUQUE, vecino de Bogotá, portador de la tarjeta profesional No. 1003, obrando como apoderado de la Sociedad COLGATE – PALMOLIVE COMPANY, según lo acredita el documento de Poder presentado en esa División bajo el No. 131, para dar cumplimiento al requerimiento notificado por fijación en lista el 5 de Septiembre de 2003 y de acuerdo con los Artículos 38 y 39 de la Decisión 486 de la Comisión de la Comunidad Andina, Artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la SIC, me permito anexar al presente escrito los siguientes documentos:

1. Documento donde consta la cesión del derecho a la Patente otorgado por los inventores al solicitante, debidamente apostillado.
2. Extracto para publicación y Tarjeta de Archivo Temático.

De la señora jefe atentamente,



RAMIRO CASTRO DUQUE

C.C. No. 170.322 de Bogotá

Código 340

Cra 7a. No. 16-56 Piso 9

Bogotá, Octubre 07, 2003

CHP/MEV/hsr

APOSTILLE

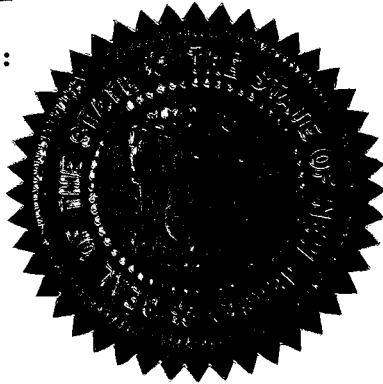
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(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
ELAINE M FLYNN
3. ACTING IN THE CAPACITY OF:
COUNTY CLERK
4. BEARS THE SEAL/STAMP OF:
COUNTY OF MIDDLESEX

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 1ST DAY OF OCTOBER 2003
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A183162
9. SEAL/STAMP:
10. SIGNATURE



A handwritten signature in cursive script, appearing to read "John E. McCormac".

STATE OF NEW JERSEY }
County of Middlesex } ss.



I, ELAINE M. FLYNN, Clerk of the County of Middlesex, do hereby certify that

CAROL M STANLEY

whose name is subscribed to the annexed certificate or proof of acknowledgment of the annexed instrument was at the time of taking the same a

NOTARY PUBLIC OF NEW JERSEY

acting in and for said county, duly commissioned and sworn, and qualified to act as such; that as such

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he was duly authorized by the laws of the State of New Jersey to take and certify depositions; to administer oaths and affirmations; to take affidavits and certify the acknowledgment and proof of deeds and other written instruments for lands, tenements and hereditaments to be read in evidence or recorded in this state; and further, that I am well acquainted with the handwriting of such

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and verify that the signature to such proof or acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the County of Middlesex, this
of Sept 29²⁰ 03

day

Elaine M Flynn

CLERK.

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COUNTY OF MIDDLESEX

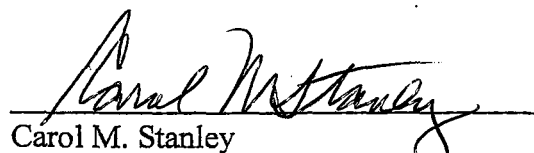
STATE OF NEW JERSEY

UNITED STATES OF AMERICA

I, Elizabeth M. Dunne, of COLGATE-PALMOLIVE COMPANY, do hereby declare that the copy attached hereto is a true photocopy of the assignment executed by the inventor(s) in support of U.S. Serial Nos. 09/568,114 filed May 10, 2000.


Elizabeth M. Dunne
International Patent Manager

Subscribed and sworn to
before me this 19th day
of April, 2001.


Carol M. Stanley
Notary Public of New Jersey
My Commission Expires November 18, 2005

Colombo

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ASSIGNMENT

WHEREAS, we (below referred to as ASSIGNORS, residing, respectively, as set forth hereinafter, have made an invention for which application for Letters Patent of the United States was filed in the United States Patent and Trademark Office as Application Serial No. 09/568,114, filed May 10, 2000 naming the ASSIGNORS as an inventor, and entitled Synergistic Antiplaque/Antigingivitis Oral Composition; and

WHEREAS, Colgate-Palmolive Company, a corporation duly organized and existing under the laws of the State of Delaware, United States of America and having its principal office and place of business at 300 Park Avenue, New York, New York 10022, and offices and place of business at 909 River Road, Piscataway, New Jersey 08855 (below referred to as "ASSIGNEE"), is desirous of obtaining the entire right, title and interest in and to the aforesaid invention and patent application and corresponding patent rights worldwide;

NOW, THEREFORE, in consideration of good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, ASSIGNORS, by these presents do sell, assign and transfer to ASSIGNEE, the full and exclusive right, title and interest in and to the aforesaid invention, the aforesaid U.S. and all corresponding foreign patent applications, all divisional, continuation, continuation-in-part, reissue and reexamination applications of the aforesaid U.S. application, and all Letters Patent or comparable rights issuing thereon in the United States and in all foreign countries, together with the right of priority under the International Convention for the Protection of Industrial Property, Inter-American Convention Relating to Patents, Designs and Industrial Models, and any other international agreements to which the United States of America adheres, and the ASSIGNORS hereby authorize and request the U.S. Commissioner of Patents and Trademarks and all foreign Patent Offices to issue all Letters Patent or comparable rights issuing on any application as aforesaid to ASSIGNEE, or to its successors, assigns or legal representatives;

ASSIGNORS hereby covenant that ASSIGNORS have full right to convey the entire interest herein assigned, and that ASSIGNORS have not executed, and will not execute, any agreement in conflict herewith;

ASSIGNORS agree to communicate to ASSIGNEE or to its successors, assigns or legal representatives any and all facts known to them or any of them respecting said invention, and without further remuneration to testify in any legal proceeding, sign all lawful papers, execute all divisional, continuation, continuation-in-part, reissue and reexamination applications, make all rightful oaths and generally do all lawful acts to aid ASSIGNEE or its successors, assigns or legal representatives to obtain and enforce proper patent protection for said invention in all countries and to enhance or perfect ASSIGNEE's title in and to the invention and patent rights therein.

ASSIGNORS hereby authorize attorneys for ASSIGNEE to enter on this document any applicable serial numbers and filing dates after ASSIGNORS' execution of this document.

This Assignment is effective as of May 10, 2000.

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 8 day of May 2000.

Dale S. Scherl

Address: 215 Kingsberry Drive
Somerset, New Jersey 08873, U.S.A.

State of New Jersey
County of Middlesex

On this 8th day of May 2000, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2000

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 5 day of May 2000.

Susan M. Herles

Address: 139 Old Clinton Road
Flemington, New Jersey 08822, U.S.A.

State of New Jersey
County of Middlesex

On this 5th day of May 2000, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

Maria V. Logatto
NOTARY PUBLIC

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2000

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 5 day of May 2000.

Address:

Tao Xu
160 Pine Street
Newton, Massachusetts 02466, U.S.A.

State of New Jersey
County of Middlesex

On this 5th day of May 2000, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2000

Maria V. Logatto
NOTARY PUBLIC

IN TESTIMONY WHEREOF, I hereunto set my hand and seal this 5 day of May 2000.

Address:

Abdul Gaffar
89 Carter Road
Princeton, New Jersey 08540, U.S.A.

State of New Jersey
County of Middlesex

On this 5th day of May 2000, before me, a Notary Public in and for the State and County aforesaid, personally appeared the above signatory, known to me to be the person of that name, who executed the foregoing instrument in my presence.

MARIA V. LOGATTO
Notary Public of New Jersey
My Commission Expires 8/8/2000

Maria V. Logatto
NOTARY PUBLIC

2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado(a)
COLGATE – PALMOLIVE COMPANY.

REFERENCIA:	Radicación N°	02-11163
	Solicitud internacional	PCT/US01/14956
	Fecha inicio fase nacional	10/12/2002
	Trámite	011
	Evento	379
	Actuación	416
	Oficio N°	927
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486.

Cúmplase
Dado en Bogotá D C,



ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202044

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 02-111663

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 543

DE FECHA 01 DE SEPTIEMBRE DE 2004 EL TERMINO HABIL SEÑALADO

POR LA LEY EXPIRA EL 29 DE NOVIEMBRE DEL 2004

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO X _____

Bogotá D.C, SEPTIEMBRE DE 2007



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 35/78, 7/26	A1	(11) International Publication Number: WO 97/35599 (43) International Publication Date: 2 October 1997 (02.10.97)
(21) International Application Number: PCT/KR97/00048 (22) International Filing Date: 26 March 1997 (26.03.97) (30) Priority Data: 1996/8393 26 March 1996 (26.03.96) KR (71) Applicant (for all designated States except US): DAEWOONG PHARMACEUTICAL CO., LTD. [KR/KR]; 223-23, Sangdaewon-dong, Joongwon-ku, Sungnam-city, Kyunggi-do 462-120 (KR). (72) Inventors; and (75) Inventors/Applicants (for US only): CHUNG, Chong-Pyoung [KR/KR]; Kaepo Woosung 4th Apartment, 3-307, Dogok 2-dong, Kangnam-ku, Seoul 135-272 (KR). BAE, Ki-Hwan [KR/KR]; 113-12, Gojeong-dong, Seo-ku, Daejeon 302-200 (KR). CHUNG, Chong-Keun [KR/KR]; Mu-goonghwa Apartment, 122-1801, Keumjeong-dong, Kunpo-city, Kyunggi-do 435-050 (KR). (74) Agents: CHOI, Kyu, Pal et al.; 824-20, Yeoksam-dong, Kangnam-ku, Seoul 135-080 (KR).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: COMPOSITION FOR PREVENTION AND TREATMENT OF PERIODONTAL DISEASES		
		
(57) Abstract The present invention relates to a composition for the prevention and treatment of periodontal disease. More specifically, the present invention relates to a composition for the prevention and treatment of periodontal disease comprising an extract of Zizyphi fructus and an extract of Magnoliae cortex. When the extract of Zizyphi fructus and the extract of Magnoliae cortex are combined in the weight ratio ranging from 1:6 to 1:12 and, preferably from 1:8 to 1:10, they together show a synergistic effect in comparison to the single use of any one of them, alone, and further exhibit an excellent effect for treatment of periodontal diseases in comparison with the agents disclosed in the prior art for prevention and treatment of periodontal diseases.		

COMPOSITION FOR PREVENTION AND TREATMENT OF PERIODONTAL DISEASES

5

TECHNICAL FIELD

The present invention relates to a composition for the prevention and treatment of periodontal diseases. More specifically, the present invention relates to a composition for the prevention and treatment of
10 periodontal diseases comprising an extract of *Zizyphi fructus* and an extract of *Magnoliae cortex*. When the extracts of *Zizyphi fructus* and *Magnoliae cortex* are combined so that the ratio of the weight of the former to the weight of the latter ranges from 1:6 to 1:12, and more particularly from 1:8 to 1:10, their combination exhibits a synergistic
15 effect in treating periodontal disease that is superior to the sum of their individual effects. Moreover, the combination is excellent for preventing and treating periodontal disease compared to agents disclosed in the prior art.

20

BACKGROUND ART

Oral diseases are generally classified as dental caries and periodontal diseases. A periodontal disease is an infectious oral disease which most frequently occurs in adult man, and results in the loss of
25 teeth due to gingival bleeding and swelling, formation of periodontal inflammation and disruption of alveolar bone, and the like. According to the currently accepted mechanism for the occurrence of periodontal disease, plaque is mechanically accumulated in periodontal pocket and then serves as a habitat for microorganisms. These microorganisms
30 gradually change from aerobic gram-positive bacteria to anaerobic gram-negative bacteria as they penetrate deep into the periodontal pocket. Fully grown anaerobic gram-negative bacteria produce toxins and other substances which directly disrupt the periodontal tissues and trigger the immunologic system. The stimulated immunological system induces the
35 disruption of alveolar bone and the inflammation of periodontal tissues

through various mechanisms. The causative microorganisms of periodontal disease are *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, etc., which are all gram-negative anaerobic bacteria normally present in the oral cavity, in contrast to the
5 causative organisms of dental caries. In addition, periodontal diseases generally occur in adult man because periodontal tissues are weakened with age.

Therefore, in order to prevent or treat the periodontal diseases, it
10 is of course preferable to eliminate all preconditions and causes of the diseases, that is, (1) to restore the weakened or disrupted periodontal tissues to their original state, (2) to remove the inflammation as the toxic production from causative microorganisms, and (3) to inhibit the reproduction of these microorganisms.

15

Studies of the prevention and treatment of periodontal disease have been conducted since the 1920's and, particularly in Europe and North America, have focussed on the antibacterial action of antibiotics and chemotherapeutic agents (for example, chlorhexidine, cetylpyridinium
20 chloride) to remove plaque.

However, the use of such antibiotics and chemotherapeutic agents has undesirable side effects such as ulceration of oral mucous membranes, induction of desquamative gingivitis, colouring, etc.

25

In addition to the antibiotics and chemotherapeutic agents, an enzyme preparation that decomposes plaque stroma, and a fluorine preparation that inhibits the adsorption of bacteria onto the surfaces of teeth have also been disclosed for preventing periodontal disease. These,
30 however, have seen limited use because the enzyme preparation has been shown to have harmful side effects and is also difficult to apply and the fluorine preparation exhibits only a weak antibacterial effect.

To overcome these disadvantages of antibiotics and other
35 synthetic medicinal products, many attempts have made to develop a

medicinal drug for treatment of periodontal disease using extracts of medicinal herbs. As a result of this work, Myrrha has been shown to be effective against gingivitis and thrush, and sanggenon C, the active component of the extract of *Mori radicis cortex*, has been shown to
5 inhibit the metabolism of *Streptococcus mutans* and thus to obstruct bacterial adhesion, which is the first step in plaque formation. However, Myrrha exhibits only a weak antibacterial effect and the extract of *Mori radicis cortex* considerably inhibits the growth of gingival fibroblast. Although the extract of *Sanguinaria* has been experimentally shown to be
10 a potent plaque inhibitor and antibacterial agent, it has not demonstrated these effects in clinical studies.

In addition, the extract of *Zea mays L.* which is marketed in Korea under the trade names Insadol (Dongkuk Pharmaceutical Co., Ltd.)
15 and Dentol (Lucky Co., Ltd.) has been used for inhibiting the inflammation of periodontal tissues.

Although such prior agents for the treatment of periodontal disease using medicinal herbs have the advantage that they have no
20 harmful side effects, their shortcomings are that they have neither an regenerative effect on damaged cells of periodontal tissue nor an antibacterial effect on causative organisms of periodontal disease.

Thus, the present inventors have intensively studied various
25 medicinal herbs in order to develop a therapeutic agent which overcomes the above mentioned disadvantages of the prior art agents for treatment of periodontal disease using medicinal herbs. As a result, the present inventors have found that the extract of *Magnoliae cortex* shows a good anti-inflammatory effect and a potent antibacterial effect on the causative
30 organisms of periodontal disease, without the harmful side effects exhibited by the prior art antibiotics (see, Korean Laid-open Patent Publication No. 94-6594) and that the extract of *Ginkgo folium* has a regenerative effect on periodontal tissues (see, Korean Laid-open Patent Publication No. 94-13606). The present inventors have also shown that
35 the combination of the extract of *Magnoliae cortex* and the extract of

Ginkgo folium is effective against periodontal diseases and, indeed, have filed a patent application relating to a composition for treatment of periodontal diseases comprising just such a combination (see, Korean Patent Application No. 94-14117). As a result of still further study, the present inventors have also identified that the extract of Zizyphi fructus is effective for regenerating periodontal tissues, and have filed a patent application relating to an agent for treatment of periodontal disease comprising the extract of Zizyphi fructus (see, Korean Patent application No. 95-14541).

10

Although the extract of Magnoliae cortex displays good anti-inflammatory and antibacterial activities, it has the disadvantage of lowering the activity of periodontal tissue cells as its dosage increases. Meanwhile, the extracts of Zizyphi fructus and Ginkgo folium together exhibit a good tissue regenerating effect but also have a weak antibacterial effect. Therefore, they are disadvantageous in view of the fact that they exhibit the effect through only some ways among various mechanisms involved in the prevention and treatment of periodontal diseases.

20

On the basis of the result of previous studies mentioned above, the present inventors have examined the efficacy of various combinations of the extracts of Magnoliae cortex and Zizyphi fructus for preventing and treating periodontal diseases. As a result, we have discovered that the combination of these two extracts at certain weight ratios shows a unexpected synergistic effect for treating periodontal diseases (i.e. excellent tissue regenerating, antibacterial and anti-inflammatory effects) and overcomes the disadvantage of the extract of Magnoliae cortex alone (i.e. inhibits the activity of periodontal tissue cells at high dosage) to provide a good tissue regenerating effect. Then, we have completed the present invention.

30

DISCLOSURE OF INVENTION

35

The present invention relates to a composition comprising the

BEST MODE FOR CARRYING OUT THE INVENTION

In the composition of the present invention, the extract of Magnoliae cortex is best obtained by extracting Magnoliae cortex with an alcohol, preferably with a lower alkanol such as ethanol. It is also preferable to use an extract of Magnoliae cortex containing at least 5.0% of magnolol and at least 1.0% of honokiol as its major ingredients. In addition, the extract of Zizyphi fructus is best obtained by extracting Zizyphi fructus with an alcohol, preferably with a lower alkanol such as ethanol, in a water bath and then concentrating the extract under reduced pressure.

The composition comprising the extracts of Zizyphi fructus and Magnoliae cortex as its active components according to the present invention exhibits a surprising synergistic effect for treating periodontal diseases when these extracts are present in specific proportions. Specifically, as demonstrated by the experiments detailed below, a synergistic effect is evident when the ratio of the weight of the extract of Zizyphi fructus to the weight of the extract of Magnoliae cortex ranges from 1:6 to 1:12, and preferably from 1:8 to 1:10.

Therefore, to maximize the synergistic therapeutic effect on periodontal diseases the composition of the present invention uses the extract of Zizyphi fructus and the extract of Magnoliae cortex in the mixing ratio ranging from 1:6 to 1:12, particularly preferably in the mixing ratio ranging from 1:8 to 1:10, on the basis of weight.

Although the composition of the present invention comprising the extracts of Zizyphi fructus and Magnoliae cortex in the mixing ratios mentioned above may be used as composed, the composition would preferably be used in pharmaceutical preparations formulated by adding conventional pharmaceutically acceptable excipients to the composition. The pharmaceutical preparations used for this purpose include tablets, ointments, solutions (gargles), sprays, etc. For example, the composition of the present invention may be included in the toothpaste or formulated

as tablets for internal use, ointments for external use, or solutions by mixing the extracts with pharmaceutically acceptable carriers.

In addition, the composition of the present invention may be included in conventional gargle preparations for washing the mouth, or it may be mixed with a propellant to prepare a spray packaged in a pressurized container and then sprayed onto the attacked periodontal portion, or it may be included in toothpaste which is used over a long period of time to obtain the preventive and therapeutic effect on periodontal diseases.

The effective dosage of the present composition can be varied depending on the purpose of use, the severity of periodontal disease to be treated, the preparation employed, etc., but is generally from 50mg to 5g, particularly from 100mg to 3g, per day for an adult man, as the combination of the extracts of *Zizyphi fructus* and *Magnoliae cortex*.

The content of the combination of the extracts of *Zizyphi fructus* and *Magnoliae cortex* in the total composition may be varied depending on the purpose of its use. However, when the content of the active ingredients is too low, the pharmaceutical effect of the composition rapidly decreases, whereas when their content is too high, the quality of the product may be reduced due to the colouring effects of the extracts of *Zizyphi fructus* and *Magnoliae cortex*. Based on the effective dosages given above, it is preferable to formulate the unit dosage form so that a tablet contains from 50mg to 250mg of the combination of the present invention and the ointment, solution (gargle), toothpaste and spray contain the combination of the present invention in the concentration of 0.2 to 5.0 wt%.

When the extracts of *Zizyphi fructus* and *Magnoliae cortex* are orally administered to mice and rats, the LD₅₀ level of each extract, which was used as the standard of acute toxicity, was determined to be 5000mg/kg or more. It is therefore evident that they are safe medicinal substances.

Composition 1 : Film coated tablet (in each 600mg tablet)

	Extract of Zizyphi fructus	20mg
	Extract of Magnoliae cortex	200mg
5	Lactose	355mg
	Hydroxypropylcellulose	5mg
	Magnesium stearate	3mg
	Glycerine	2mg
	Hydroxypropylmethylcellulose	15mg

10

The tablet was prepared from the above mentioned components using conventional method for preparing tablets.

Composition 2 : Ointment (in wt%)

15

	Extract of Zizyphi fructus	0.04
	Extract of Magnoliae cortex	0.32
	Carboxyvinyl polymer	7.00
	Glycerol	30.00
20	Peppermint oil	0.006
	Propylene glycol	30.00
	Purified water to make	100.

The ointment was prepared from the above mentioned components using the conventional method for preparing ointments.

Composition 3 : Toothpaste (in wt%)

	Extract of Zizyphi fructus	0.04
30	Extract of Magnoliae cortex	0.40
	Alumina	45.00
	Propylene glycol	10.00
	Carboxymethylcellulose sodium	2.00
	Stevioside	0.30
35	Sodium lauryl sulfate	1.00

12

Peppermint	0.50
Purified water to make	100.

5 The above components were mixed using conventional method for preparing toothpastes.

Composition 4 : Solution (in wt%)

10	Extract of Zizyphi fructus	0.08
	Extract of Magnoliae cortex	0.96
	Polyethylene glycol	7.00
	Ethanol	5.00
	Peppermint oil	0.06
	Purified water to make	100.

15

The solution was prepared by mixing and dissolving the above mentioned components and then adjusting the pH value to 5.0 using conventional method for preparing solutions.

20 **Composition 5 : Spray (in wt%)**

25	Extract of Zizyphi fructus	0.04
	Extract of Magnoliae cortex	0.24
	Trichloromonofluoromethane	40.00
	Dichlorodifluoromethane	45.00
	Peppermint oil	0.15
	Ethanol	6.00
	Polyethylene glycol	8.65

30 The spray was prepared by mixing the above mentioned components and then packaging the mixture into a pressurized container using conventional method for preparing sprays.

35 **Experiment : Determination of the mixing ratio of the extract of Zizyphi fructus and the extract of Magnoliae cortex**

WHAT IS CLAIMED IS :

1. A composition for the prevention and treatment of periodontal diseases which comprises an alcohol extract of Zizyphi fructus and an alcohol extract of Magnoliae cortex wherein the ratio of the weight of the extract of Zizyphi fructus to the weight of the extract of Magnoliae cortex ranges from 1:6 to 1:12.
2. The composition as defined in claim 1, wherein the ratio of the weight of the alcohol extract of Zizyphi fructus and the weight of the alcohol extract of Magnoliae cortex ranges from 1:8 to 1:10.
3. The composition as defined in claim 1 or 2, wherein the alcohol extract of Zizyphi fructus and the alcohol extract of Magnoliae cortex are ethanol extracts thereof.
4. The composition as defined in claim 1, which is formulated in a pharmaceutical unit dosage form using an additional pharmaceutically acceptable carrier.
5. The composition as defined in claim 4, wherein the pharmaceutical unit dosage form is tablet, ointment, toothpaste, solution (gargle) or spray.
6. The composition as defined in claim 5, which contains from 50mg to 250mg of the combination of the extract of Zizyphi fructus and the extract of Magnoliae cortex per tablet.
7. The composition as defined in claim 5, which contains the combination of the extract of Zizyphi fructus and the extract of Magnoliae cortex in the concentration of 0.2 to 5.0 wt% per unit dosage form of ointment, toothpaste, solution (gargle) or spray.



US005188821A

United States Patent [19]
Gaffar et al.

[11] **Patent Number:** **5,188,821**
[45] **Date of Patent:** * **Feb. 23, 1993**

- [54] **ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION MOUTHWASH OR LIQUID DENTIFRICE**
- [75] **Inventors:** Abdul Gaffar, Princeton; Nuran Nabl, North Brunswick; John Afflitto, Brookside, all of N.J.; Orum Stringer, Yardley, Pa.
- [73] **Assignee:** Colgate-Palmolive Company, Piscataway, N.J.
- [*] **Notice:** The portion of the term of this patent subsequent to Jan. 16, 2007 has been disclaimed.
- [21] **Appl. No.:** 398,592
- [22] **Filed:** Aug. 28, 1989

Related U.S. Application Data

- [63] Continuation-in-part of Ser. No. 291,712, Dec. 29, 1988, Pat. No. 4,894,220, and a continuation-in-part of Ser. No. 346,258, May 1, 1989, Pat. No. 5,043,154, which is a continuation of Ser. No. 8,901, Jan. 30, 1987, abandoned, said Ser. No. 291,712, is a continuation-in-part of Ser. No. 8,901.
- [51] **Int. Cl.³** A61K 7/16; A61K 7/18
- [52] **U.S. Cl.** 424/52; 424/49; 106/35; 523/118; 526/936
- [58] **Field of Search** 424/49-58; 106/35; 523/116, 118, 120; 526/936

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[57] **ABSTRACT**

An oral composition mouthwash or liquid dentifrice containing an aqueous vehicle acceptable vehicle, a substantially water-insoluble noncationic antibacterial antiplaque agent, such as 2,4,4'-trichloro-2'-hydroxydiphenyl ether (triclosan) and an antibacterial-enhancing agent which enhances delivery of said antibacterial agent to, and retention thereof on, oral surfaces.

21 Claims, No Drawings

5,188,821

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ANTIBACTERIAL ANTIPLAQUE ORAL COMPOSITION MOUTHWASH OR LIQUID DENTIFRICE

This application is a continuation-in-part of application Ser. No. 07/291,712, filed Dec. 29, 1988 and now U.S. Pat. No. 4,894,220 and of application Ser. No. 07/346,258 filed May 1, 1989 and now U.S. Pat. No. 5,043,154, which are respectively a continuation-in-part and a continuation of application Ser. No. 07/008901, filed Jan. 30, 1987 now abandoned.

This invention relates to an antibacterial antiplaque oral composition mouthwash or liquid dentifrice. More particularly, it relates to an oral composition mouthwash or liquid dentifrice containing a substantially water-insoluble noncationic antibacterial agent effective to inhibit plaque.

Dental plaque is a soft deposit which forms on teeth as opposed to calculus which is a hard calcified deposit on teeth. Unlike calculus, plaque may form on any part of the tooth surface, particularly including at the gingival margin. Hence, besides being unsightly, it is implicated in the occurrence of gingivitis.

Accordingly, it is highly desirable to include antimicrobial agents which have been known to reduce plaque in oral compositions. Frequently, cationic antibacterial agents have been suggested. Moreover, in U.S. Pat. No. 4,022,880 to Vinson et al, a compound providing zinc ions as an anticalculus agent is admixed with an antibacterial agent effective to retard the growth of plaque bacteria. A wide variety of antibacterial agents are described with the zinc compounds including cationic materials such as guanides and quaternary ammonium compounds as well as non-cationic compounds such as halogenated salicylanilides and halogenated hydroxydiphenyl ethers. The noncationic antibacterial antiplaque halogenated hydroxydiphenyl ether, triclosan, has also been described in combination with zinc citrate trihydrate in European Patent Publication 0161,899 to Saxton et al. Also, in European Patent Publication 0271,332 to Davis, mouthwash containing triclosan and in a carrier system containing a solubilizing agent such as propylene glycol is disclosed.

The cationic antibacterial materials such as chlorhexidine, benzthionium chloride and cetyl pyridinium chloride have been the subject of greatest investigation as antibacterial antiplaque agents. However, they are generally not effective when used with anionic materials. Noncationic antibacterial materials, on the other hand, can be compatible with anionic components in an oral composition.

However, oral compositions typically are mixtures of numerous components and even such typically neutral materials as humectants can affect performance of such compositions.

Moreover, even noncationic antibacterial antiplaque agents may have limited antiplaque effectiveness with commonly employed materials such as polyphosphate anticalculus agents which are disclosed together in British Patent Publication 2200551 of Gaffar et al and EP 0251591 of Jackson et al. In commonly assigned Ser. No. 398,605 filed Aug. 25, 1989, titled "Antibacterial, Antiplaque Anticalculus Oral Composition", it is shown that the antiplaque effectiveness is greatly enhanced by including an antibacterial-enhancing agent (AEA) which enhances the delivery of said antibacterial agent to, and retention thereof on, oral surfaces and providing

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optimized amounts and ratios of polyphosphate and AEA.

Further, even when polyphosphate anticalculus agent is not present as shown in patent applications commonly assigned Ser. Nos. 398,606; 398,566; and 399,699 each filed on Aug. 25, 1989, antiplaque effectiveness on soft oral tissue is optimized in dentifrices containing the noncationic antibacterial agent and said AEA.

It is an advantage of this invention that an oral composition mouthwash or liquid dentifrice is obtained in which substantially water-insoluble noncationic antibacterial agent is solubilized to provide substantial antiplaque effectiveness in the presence of said AEA.

It is an advantage of this invention that the said AEA enhances the delivery and retention of small but effective antiplaque amount of the antibacterial agent on teeth and on soft oral tissues.

It is a further advantage of this invention that an antiplaque oral composition is provided which is directly or indirectly effective to reduce the occurrence of gingivitis.

Additional advantages of this invention will be apparent from consideration of the following specification.

In accordance with certain of its aspects, this invention relates to an oral composition dentifrice comprising in an orally acceptable vehicle, an effective antiplaque amount of a substantially water insoluble noncationic antibacterial agent, and about 0.05-4% by weight of said AEA, wherein said oral composition comprises a solubilizing material for said antibacterial agent in amount sufficient to dissolve said antibacterial agent in saliva.

Typical examples of water insoluble noncationic antibacterial agents which are particularly desirable from considerations of antiplaque effectiveness, safety and formulation are:

Halogenated Diphenyl Ethers

2',4,4'-trichloro-2'-hydroxy-diphenyl ether (Triclosan)
2,2'-dihydroxy-5,5'-dibromo-diphenyl ether.

Halogenated Salicylanilides

4',5-dibromosalicylanilide
3,4',5-trichlorosalicylanilide
3,4',5-tribromosalicylanilide
2,3,3',5-tetrachlorosalicylanilide
3,3,3',5-tetrachlorosalicylanilide
3,5-dibromo-3'-trifluoromethyl salicylanilide
5-n-octanoyl-3'-trifluoromethyl salicylanilide
3,5-dibromo-4'-trifluoromethyl salicylanilide
3,5-dibromo-3'-trifluoro methyl salicylanilide (Fluorophene)

Benzoic Esters

Methyl	p-Hydroxybenzoic Ester
Ethyl	p-Hydroxybenzoic Ester
Propyl	p-Hydroxybenzoic Ester
Butyl	p-Hydroxybenzoic Ester

Halogenated Carbanilides

3,4,4'-trichlorocarbanilide
3-trifluoromethyl-4,4'-dichlorocarbanilide
3,3,4'-trichlorocarbanilide

Halogenated Carbanilides

3,4,4'-trichlorocarbanilide

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3-trifluoromethyl-4,4'-dichlorocarbaniide
3,3,4'-trichlorocarbaniide

Phenolic Compounds (including phenol and its homologs, mono- and poly-alkyl and aromatic halo (e.g. F, Cl, Br, I)-phenols, resorcinol and catechol and their derivatives and bisphenolic compounds). Such compounds include inter alia:

Phenol and its Homologs

Phenol	
2 Methyl	Phenol
3 Methyl	Phenol
4 Methyl	Phenol
4 Ethyl	Phenol
2,4-Dimethyl	Phenol
2,5-Dimethyl	Phenol
3,4-Dimethyl	Phenol
2,6-Dimethyl	Phenol
4-n Propyl	Phenol
4-n Butyl	Phenol
4-n Amyl	Phenol
4-tert-Amyl	Phenol
4-n-Hexyl	Phenol
4-n-Heptyl	Phenol
2-Methoxy-4-(2-Propenyl)	Phenol (Eugenol)
2-Isopropyl-5-Methyl	Phenol (Thymol)

Mono- and Poly-Alkyl and Aalkyl Halophenols

Methyl	p-Chlorophenol
Ethyl	p-Chlorophenol
n-Propyl	p-Chlorophenol
n-Butyl	p-Chlorophenol
n-Amyl	p-Chlorophenol
sec-Amyl	p-Chlorophenol
n-Hexyl	p-Chlorophenol
Cyclohexyl	p-Chlorophenol
n-Heptyl	p-Chlorophenol
n-Octyl	p-Chlorophenol
<u>O-Chlorophenol</u>	
Methyl	o-Chlorophenol
Ethyl	o-Chlorophenol
n-Propyl	o-Chlorophenol
n-Butyl	o-Chlorophenol
n-Amyl	o-Chlorophenol
tert-Amyl	o-Chlorophenol
n-Hexyl	o-Chlorophenol
n-Heptyl	o-Chlorophenol
<u>p-Chlorophenol</u>	
o-Benzyl	p-Chlorophenol
o-Benzyl-m-methyl	p-Chlorophenol
o-Benzyl-m,m-dimethyl	p-Chlorophenol
o-Phenylethyl	p-Chlorophenol
o-Phenylethyl-m-methyl	p-Chlorophenol
3-Methyl	p-Chlorophenol
3,5-Dimethyl	p-Chlorophenol
6-Ethyl-3-methyl	p-Chlorophenol
6-n-Propyl-3-methyl	p-Chlorophenol
6-iso-propyl-3-methyl	p-Chlorophenol
2-Ethyl-3,5-dimethyl	p-Chlorophenol
6-sec Butyl-3-methyl	p-Chlorophenol
2-iso-Propyl-3,5-dimethyl	p-Chlorophenol
6-Diethylmethyl-3-methyl	p-Chlorophenol
6-iso-Propyl-2-ethyl-3-methyl	p-Chlorophenol
2-sec Amyl-3,5-dimethyl	p-Chlorophenol
2-Diethylmethyl-3,5-dimethyl	p-Chlorophenol
6-sec Octyl-3-methyl	p-Chlorophenol
<u>p-Bromophenol</u>	
Methyl	p-Bromophenol
Ethyl	p-Bromophenol
n-Propyl	p-Bromophenol
n-Butyl	p-Bromophenol
n-Amyl	p-Bromophenol
sec-Amyl	p-Bromophenol
n-Hexyl	p-Bromophenol
cyclohexyl	p-Bromophenol

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-continued

<u>o-Bromophenol</u>	
tert-Amyl	o-Bromophenol
n-Hexyl	o-Bromophenol
n-Propyl-m,m-Dimethyl	o-Bromophenol
2-Phenyl Phenol	
4-Chloro-2-methyl phenol	
4-chloro-3-methyl phenol	
4-chloro-3,5-dimethyl phenol	
2,4-dichloro-3,5-dimethyl phenol	
3,4,5,6-tetrabromo-2-methylphenol	
5-methyl-2-pentylphenol	
4-isopropyl-3-methylphenol	
5-chloro-2-hydroxydiphenyl methane	

Resorcinol and Its Derivatives

<u>Resorcinol</u>	
Methyl	Resorcinol
Ethyl	Resorcinol
n-Propyl	Resorcinol
n-Butyl	Resorcinol
n-Amyl	Resorcinol
n-Hexyl	Resorcinol
n-Heptyl	Resorcinol
n-Octyl	Resorcinol
n-Nonyl	Resorcinol
Phenyl	Resorcinol
Benzyl	Resorcinol
Phenylethyl	Resorcinol
Phenylpropyl	Resorcinol
p-Chlorobenzyl	Resorcinol
5-Chloro	2,4-Dihydroxydiphenyl Methane
4'-Chloro	2,4-Dihydroxydiphenyl Methane
5-Bromo	2,4-Dihydroxydiphenyl Methane
4'-Bromo	2,4-Dihydroxydiphenyl Methane

Bisphenolic Compounds

Bisphenol A

2,2'-methylene bis (4-chlorophenol)

2,2'-methylene bis (3,4,6-trichlorophenol) (hexachlorophene)

2,2'-methylene bis (4-chloro-6-bromophenol)

bis (2-hydroxy-3,5-dichlorophenyl) sulfide

bis (2-hydroxy-5-chlorobenzyl) sulfide

The noncationic antibacterial agent is present in the oral composition in an effective antiplaque amount, typically about 0.01-5% by weight although in a mouthwash or liquid dentifrice the amount is generally about 0.01-0.3%, preferably about 0.03-0.3% and more preferably about 0.03-0.1%. The antibacterial agent is substantially water-insoluble, meaning that its solubility is less than about 1% by weight in water at 25° C. and may be even less than about 0.1%.

The preferred halogenated diphenyl ether is triclosan. The preferred phenolic compounds are phenol, thymol, eugenol, and 2,2'-methylene bis(4-chloro-6-bromophenol). The most preferred antibacterial antiplaque compound is triclosan. Triclosan is disclosed in aforementioned U.S. Pat. No. 4,022,880 as an antibacterial agent in combination with an anticalculus agent which provides zinc ions and in German Patent Disclosure 3532860 in combination with a copper compound. In European Patent Disclosure 0278744 it is disclosed in combination with a tooth desensitizing agent containing a source of potassium ion. It is also disclosed as an antiplaque agent in a dentifrice formulated to contain a lamellar liquid crystal surfactant phase having a lamellar spacing of less than 6.0 nm and which may optionally contain a zinc salt in published European Patent

	A Parts	B Parts	C Parts	D Parts	E Parts
Gantrez S-97	0.25	0.25	0.25	0.25	0.25
Glycerine	15.00	10.00	15.00	10.00	15.00
Ethanol	—	—	12.50	12.50	—
Propylene glycol	—	5.00	—	5.00	—
Pluronic F108- (Polyoxyethylene/ Polyoxypropylene Block Copolymer)	—	2.00	—	—	—
Sodium Lauryl Sulfate	—	—	0.20	0.20	0.20
Triclosan	0.10	0.10	0.06	0.06	0.03
Flavoring oil	0.40	0.40	0.40	0.40	0.40
Water	Q.S. to 100.00	Q.S. to 100.00	Q.S. to 100.00	Q.S. to 100.00	Q.S. to 100.00

EXAMPLE 2

The following liquid dentifrices are also effective in reducing plaque by increasing the uptake and retention of triclosan on oral surfaces:

	A Parts	B Parts	C Parts
Glycerine	20.0	20.0	—
Gantrez S-97	0.3	0.3	0.3
Polysaccharide of high molecular weight, the molecule containing mannose, glucose, potassium glucuronate and acetyl moieties in the approximate molar ratio of 2:1:1:1	0.8	—	1.0
Sodium benzoate	0.5	0.5	0.5
Saccharine sodium	0.5	0.5	0.5
Water	61.3	73.1	71.6
Sodium lauryl sulfate	3.0	3.0	3.0
Insoluble sodium metal phosphate	10.0	—	10.0
Anhydrous dicalcium phosphate	1.0	—	2.5
Flavoring oil	2.5	2.5	2.5
Ethyl alcohol	—	—	10.0
Triclosan	0.1	0.1	0.1

In the foregoing Examples improved results are also achievable when triclosan is replaced with each of phenol, 2,2'-methylene bis (4-chloro-6-Bromophenol), eugenol and thymol, and/or when Gantrez is replaced by other AEA's such as Carbopols (e.g. 934), or styrene phosphonic acid polymers having molecular weights within the range of about 3,000 to 10,000 such as poly (beta-styrenephosphonic acid), copolymers of vinyl phosphonic acid with beta-styrenephosphonic acid, and poly (alpha-styrenephosphonic acid), or sulfoacrylic oligomers, or a 1:1 copolymer of maleic anhydride with ethyl acrylate.

This invention has been described with respect to certain preferred embodiments and it will be understood that modifications and variations thereof obvious to those skilled in the art are to be included within the purview of this application and the scope of the appended claims.

We claim:

1. In a method of preparing an oral composition mouthwash or liquid dentifrice wherein delivery and retention of a plaque-inhibiting antibacterial agent is enhanced by attaching, adhering or bonding to oral tooth and gum surfaces comprising an aqueous vehicle, an effective amount in the range of about 0.15-5% by weight of substantially water insoluble noncationic antibacterial agent and at least one of a surface active agent, a flavoring oil or a non-toxic alcohol, the improvement comprising employing in said composition about 0.05-4% by weight of a water-soluble or swellable antibacterial-enhancing agent, which contains at least one

delivery-enhancing functional group and at least one organic retention-enhancing group, wherein said delivery-enhancing group enhances delivery of said antibacterial agent to oral tooth and gum surfaces and said retention-enhancing group enhances attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount.

2. In a method of attaching, adhering or bonding a plaque-inhibiting antibacterial agent to oral tooth and gum surfaces comprising applying to oral surfaces, an oral composition mouthwash or liquid dentifrice comprising an aqueous vehicle and an effective amount in the range of about 0.01-5% by weight of substantially water insoluble noncationic antibacterial agent and at least one of a flavoring oil or a non-toxic alcohol, the improvement comprising employing in said composition an effective amount in the range of about 0.05-4% by weight of a water-soluble or swellable antibacterial-enhancing agent which contains at least one delivery-enhancing functional group and at least one organic retention-enhancing group, which delivery-enhancing group enhances delivery of said antibacterial agent to oral tooth and gum surfaces, and said retention-enhancing agent enhances attachment, adherence or bonding of said antibacterial agent on oral tooth and gum surfaces, wherein said oral composition is free of polyphosphate anticalculus agent in an effective anticalculus amount.

3. The method claimed in either of claims 1 or 2 wherein said antibacterial agent is a halogenated diphenyl ether.

4. The method claimed in claim 3 wherein said halogenated diphenyl ether is 2,4,4'-trichloro-2'-hydroxydiphenyl ether.

5. The method claimed in either of claims 1 or 2 wherein said amount of antibacterial agent is about 0.25-0.5%.

6. The method claim in either of claims 1 or 2 wherein said composition is a mouthwash and said aqueous vehicle contains a non-toxic alcohol and the weight ratio of water to non-toxic is from about 1:1 to about 20:1.

7. The method claimed in claim 6 wherein said non-toxic alcohol is ethanol.

8. The method claimed in either of claims 1 or 2 wherein said surface active agent is present in amount of about 0.5-5% by weight.

9. The method claimed in either of claims 1 or 2 wherein said flavoring oil is present in amount of about 0.1-5% by weight.

10. The method claimed in either of claims 1 or 2 wherein said antibacterial-enhancing agent has an average molecular weight of about 100 to about 1,000,000.

11. The method claimed in claim 10 wherein said delivery enhancing group is acidic.

12. The method according to claim 11 wherein said delivery-enhancing group is selected from the group consisting of carboxylic, phosphonic, phosphonic, and sulfonic acids, and their salts, and mixtures thereof and wherein said retention-enhancing group comprises the formula $-(X)_n-R$ wherein X is O, N, S, SO, SO₂, P, PO or Si, R is hydrophobic alkyl, alkenyl, acyl, aryl, alkaryl, aralkyl, heterocyclic, or their inert-substituted derivatives, and n is zero or 1 or more and wherein said antibacterial enhancing agent is a natural or synthetic polymerizable monomer or a polymer selected from the

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

202078
Bogotá, D.C., 21, 09, 2007

Abogado
RAMIRO CASTRO DUQUE
Apoderado
Solicitante: COLGATE-PALMOLIVE COMPANY.

ASUNTO	Radicación	02111663
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	12573
	Folios	18

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1. Descripción: Folios: 94 a 112 como se radicó inicialmente
- 1.2. Reivindicaciones: 1 a 16 Folios 113 a 115 como se radicó inicialmente.
1 a 6 Folio 139 en caso de haberse hecho alguna modificación.
- 1.3. Prioridad: (10 DE MAYO DE 2000, US y 09/568,144).

2. Objeto de la invención

Título de la solicitud: **COMPOSICION SINERGISTICA ANTIPLACA-ANTINGINGIVITIS.**

Reivindicaciones 1–6: Composiciones orales que contienen un vehículo y una cantidad antiplaca efectiva de una combinación de un éter hidroxidifenil halogenado no catiónico y un extracto de corteza de magnolia officinalis.

El problema planteado en esta solicitud es que los compuestos antibacteriales catiónicos (clorhexidina, cloruro de benzotonio y cloruro de cetil piridinio) no son efectivos cuando también esta presente en la composición oral, un tensioactivo aniónico requerido para el desempeño efectivo de las composiciones tales como pastas dentales y enjuagues bucales)

Para solucionar este problema técnico la solicitud en estudio reconoce la necesidad de proporcionar: una composición, dentífrico antiplaca, donde una combinación de

un agente no herbáceo y un ingrediente herbáceo, exhibe una actividad antiplaca sinérgica dando como resultado mejorada efectividad contra la gingivitis.

- Clasificación Internacional de Patentes (IPC): A61K 7/16, 7/26.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

La reivindicación 1 es muy amplia y no es concisa por cuanto se pueden obtener muchas composiciones orales, al combinar vehículos oralmente aceptables y una combinación de un éter hidroxidifenil halogenado no catiónico con un extracto de corteza de magnolia. La expresión "cantidad antiplaca efectiva" es ambigua e imprecisa.

La reivindicación 2 menciona que el difenil éter halogenado no iónico esta presente en la composición oral, en una cantidad en el rango de alrededor de 0,003 hasta alrededor de 2,0% en peso, no es concisa y es muy amplia.

La reivindicación 6 menciona que el extracto de magnolia esta presente en la composición en una cantidad, en el rango de alrededor de 0,001 hasta alrededor de 10% en peso, no es concisa y es muy amplia.

En el ejemplo I de la descripción (folio 108) se menciona una solución etanólica al 0,3% del extracto de magnolia y 0,3% de solución en etanol de triclosan, con la cual se realizo el ensayo de concentraciones inhibitorias mínima (MIC) y la determinación del valor de la concentración inhibitoria fraccional (FIC) para comprobar la eficacia antibacterial de la combinación de extracto de magnolia y triclosan, la cual mostró **sinergismo a esas concentraciones** (tabla I).

Además el ejemplo II de la descripción (folio 110) que menciona **una composición B**, con 0,3% triclosan y 0,3% del extracto de magnolia, correspondiente al ensayo para evaluar el grado de inflamación gingival, de acuerdo con el sistema de índice gingival, mostro una reducción representativa de la gingivitis frente a la composición A que no contiene el extracto de magnolia (tabla III) .

Se observa que estos ejemplos **no sustentan las reivindicaciones anteriormente citadas**, porque en ellas se pretende reivindicar composiciones orales con concentraciones, por encima de 0,3%, para los dos ingredientes utilizados, triclosan hasta alrededor de 2.0% y extracto de magnolia hasta alrededor de 10%.

Por lo anteriormente expuesto, se solicita al interesado cumplir con el requisito de claridad y concisión en las reivindicaciones citadas.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 10 de mayo de 2000, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

N°	Documento	Título	Fecha de publicación*
D1	WO9735599	Composition for prevention and treatment of periodontal diseases	Octubre 2 de 1997
D2	US 5188821	Antibacterial antiplaque oral composition mouthwash or liquid dentifrice Composition for prevention and treatment of periodontal diseases	Febrero 23 de 1993

5. Análisis de patentabilidad (según requisito) (artículo 14 D486)

5.1. Nivel inventivo (artículo 18 D486)

Las Reivindicaciones 1-6, mencionan composiciones orales **antigengivitis** que comprenden un vehículo oralmente aceptable y una cantidad antiplaca efectiva de una combinación de un éter hidroxidifenil halogenado no catiónico (**triclosan**) y un **extracto de corteza de magnolia officinalis**.

D1 enseña una composición que tienen como ingredientes: extractos de *zizyphi fructus* y de **magnoliae cortex**, mostrando un efecto **sinérgico** cuando están en combinación, con un excelente efecto para el tratamiento de enfermedades periodontales (folios: 155, pg 4 reglones 21-31; 156, pg 8 reglones 1-35; 157 pg 9, reglones 5-30; 158y159 pgs 11 y 12; 160 pg 29, reivindicaciones 1,4,5 y 6); que sirven para el mismo propósito: **prevención y tratamiento de enfermedades periodontales (gengivitis)**, que la Invención reivindicada.

La única diferencia con D1 es que en la solicitud reivindicada, la composición citada, contiene un éter hidroxidifenil halogenado no catiónico (**triclosan**) a cambio del **extracto de zizyphi fructus**.

El efecto técnico que logra la diferencia no puede determinarse porque los ejemplos I y II de la descripción **no sustentan el capítulo reivindicatorio**.

Por lo cual Problema Técnico Objetivo fundamental de la Invención Reivindicada no puede definirse y las composiciones reivindicadas se consideran tan solo alternativas, sin un efecto sorprendente, que las haga superiores a **las composición previamente conocidos en D1**.

D1 enseña sinergia entre dos extractos herbáceos, de manera que la sinergia de la composición obtenida al sustituir el extracto de *zizyphi fructus* por un éter hidroxidifenil halogenado no catiónico (**triclosan**) en la composición de: extracto de *zizyphi fructus* y de **magnoliae cortex**, cuyo excelente efecto **antibacterial y antiplaca, para el tratamiento de enfermedades periodontales (gengivitis)**, se había divulgado en D2 (folios: 161 abstract, 162 columna 1, reglones 14-18 y columna 2 reglones 26-29 y 40, 163, columna 4, reglones 153 y 154; 164, columna 15 ejemplos 1 y 2), no es inesperada para el Experto en la Materia, ya que este lo lograría fácilmente.

La necesidad de proveer composiciones para incrementar sinérgicamente los efectos para el tratamiento de enfermedades periodontales (antiplaca-antigengivitis)

se había resuelto previamente mediante el mismo tipo de composiciones ya conocidas.

Debido a que los documentos D1 y D2, pertenecen al mismo campo técnico, para el experto en la materia era obvio combinarlos y así llegar a obtener las composiciones reivindicadas en la presente solicitud.

Por lo cual las combinaciones de esta solicitud no tienen nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento Nº	Reivindicaciones afectadas	Requisito que afecta
D1	WO9735599	1-6	Nivel inventivo
D2	US 5188821	1-6	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única Nº 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 05/07/2015

CONCEPTO TÉCNICO No.1675	EXAMINADOR TÉCNICO Código No.202078
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