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Industria y Comercio
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

SOLICITANTE
(71)

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Lugar de Constitución: Estados Unidos

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IDENTIFICACION

C.C.



NIT



C.E.



Otro



Cual

Número

3

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O APODERADO

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NIT



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Cual

Número 170.322 TP 1003

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Nacionalidad o Domicilio: Estados Unidos de América

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Fecha 15-11-2001

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(33) País de Origen

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

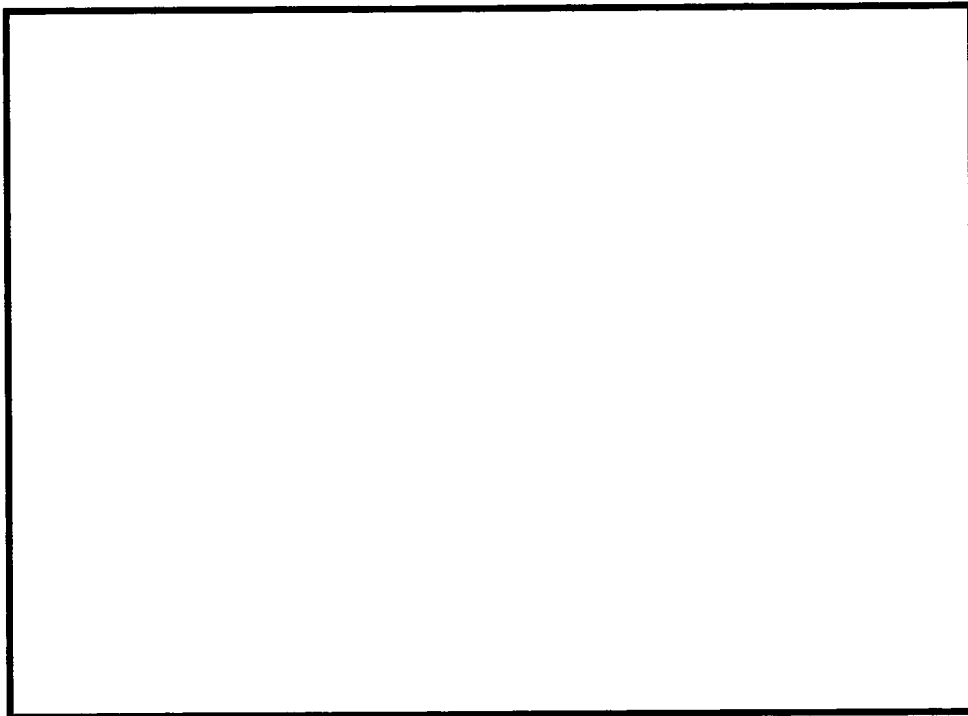
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$378.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$106.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Protocolo No. 131
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.



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SUPERINTENDENCIA

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BA & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	1326765	28/10/2002	3,995,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	83 INVOCACION DE UNA PRIORIDAD EN SI	53,000.00
	TOTAL :	\$ 53,000.00

SON: CINCUENTA Y TRES MIL PESOS

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Industria y Comercio

SUPERINTENDENCIA

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BR & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	1326765	28/10/2002	3,995,000.00

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		TOTAL :	\$ 53,000.00

SON: CINCUENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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***** CONCEPTO *****

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1 30003-01-01 SOLICITUDES	1 TRAMITE DE SOL. DE PATENTE DE IN	378,000.00
	TOTAL :	\$ 378,000.00

SON: SEISCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE :

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- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: SYNERGISTIC ANTIPLAQUE/ANTINGINGIVITIS ORAL COMPOSITION

(57) Abstract: An oral care composition containing a synergistic antiplaque/antigingivitis combination of a nonionic halogenated diphenyl ether compound such as Triclosan and an extract of Magnolia Officinalis containing honokiol and magnolol.

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SYNERGISTIC ANTIPLAQUE/ANTINGIVITIS ORAL COMPOSITION

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BACKGROUND OF THE INVENTION1. Field of the Invention

10 This invention relates to a antiplaque combination of a noncationic halogenated hydroxydiphenyl ether antibacterial agent and an extract of Magnolia Officinalis and more particularly to an oral composition containing such combination which exhibits increased antingivitis effect due to synergistic antibacterial effect against plaque bacteria.

2. The Prior Art

15 It is difficult to predict the antiplaque efficacy of antibacterial compounds when incorporated in a delivery vehicle and particularly in oral compositions. For example, 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 at the gingival margin and is implicated in the occurrence of gingivitis. Cationic antibacterial compounds such as chlorhexidine, benzothonium chloride and cetyl pyridinium
20 chloride have been used by the art as antibacterial antiplaque agents in oral compositions. However, such agents are generally not effective when there is also present in the oral composition an anionic surfactant required for the effective performance of oral compositions such as toothpaste and mouthrinses.

25 Noncationic antibacterial materials are compatible with anionic surfactants in oral compositions and noncationic halogenated hydroxydiphenyl ethers such as Triclosan have been effectively employed in commercial oral compositions as antiplaque agents when mixed with neutral ingredients such as humectants, abrasives and thickeners conventionally used in the formulation of oral compositions. Notwithstanding the efficacy of halogenated
30 hydroxydiphenyl ethers such as Triclosan, there is a continuing interest in the oral care field for agents which improve the efficacy of such noncationic halogenated hydroxydiphenyl ethers.

35 Recently, interest has been displayed in the medicinal properties of herbal preparations for use in oral compositions. Herbal preparations are considered "more natural" and are therefore viewed as more acceptable antibacterial ingredients to the consumer.

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Extracts of Magnolia Cortex (barks of *Magnolia officinalis*) are known to have antibacterial efficacy. For example, it has been reported in "Dental caries Prevention by Traditional Chinese Medicines", T. Namba et al, J. Medicinal Plant Res., vol. 44, pp. 100-106(1982) that some active principles of these extracts, identified to be magnolol and honokiol, were bactericidal against *S. mutans* in the in vitro test Minimal Inhibitory Concentration (MIC) but was not found to be inhibitory to plaque adherence to teeth in vitro tests designed to determine the therapeutic efficacy of antiplaque antigingivitis.

The dental art is continuously seeking synergistic enhancement of antiplaque/antigingivitis of non-herbal, antibacterial compositions such as halogenated biphenylether using herbal compositions in which the non-herbal ingredient has high antibacterial activity alone, while the herbal ingredient has little or no antiplaque activity, wherein the two ingredients have far higher antiplaque activity than could be expected from their individual activities, thus displaying synergism. The advantage of such synergism is that the effectiveness of the non-herbal antiplaque agent is greatly increased, without a concomitant increase in the dosage level or rate of administration so that lower quantities of the non-herbal antiplaque agent can be administered, yet still achieve the desired therapeutic effect. Such synergistic combinations are particularly important in the treatment of delicate or sensitive tissues, such as the oral mucosa, where the ability to reduce the level of the non-herbal antiplaque agent in the oral composition would be beneficial.

There is thus a recognized need for, and it would be highly advantageous to have a antiplaque dentifrice in which a combination of a non-herbal antiplaque agent and a herbal ingredient exhibited synergistic antiplaque activity resulting into enhanced effectiveness against gingivitis.

SUMMARY OF THE INVENTION

In accordance with the present invention it has been unexpectedly discovered that a combination of a nonionic halogenated hydroxydiphenyl ether such as Triclosan and phenolic compound selected from magnolol and honokiol and mixtures thereof extracted from the cortex of *Magnolia Officinalis* hereinafter referred to as "Magnolia Extract", are synergistically effective in inhibiting the growth of plaque causing bacteria whereby enhanced antiplaque activity in substantial excess of the additive antibacterial effect of the individual noncationic halogenated hydroxydiphenyl ether or Magnolia Extract is exhibited by the combination of these agents.

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The fact that halogenated hydroxydiphenyl ether compounds such as Triclosan have been approved as safe and effective for use in oral care products and that the Magnolia Extract is a widely used herbal extract, particularly in Chinese medicine, suggests that these compounds will both be commercially acceptable as ingredients in oral hygiene products such as dentifrice, mouth rinse, chewing gum and lozenge formulations.

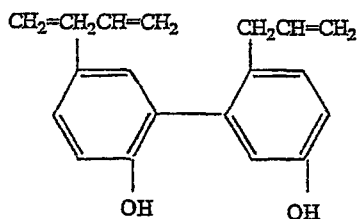
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The Magnolia Extract of the present invention is a dried cortex extract of *Magnolia officinalis* which belongs to the family Magnoliaceae. As used herein, "extracting" or "extraction" of a solid or liquid material means contacting the material, which if solid is preferably dried and crushed or ground, with an appropriate solvent to remove the substance(s) desired to be extracted from the material. Such an extraction may be carried out by conventional means; for example, by using an extraction apparatus, such as a Soxhlet apparatus, which retains the solid material in a holder and allows the solvent to flow through the material; or by blending the solvent and material together and then separating the liquid and solid phases or two immiscible liquid phases, such as by filtration or by settling and decanting.

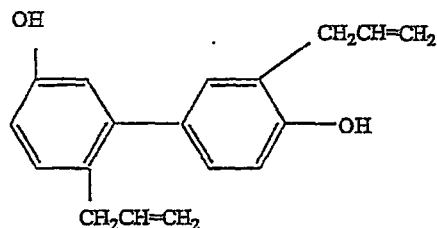
Preferred Magnolia Extracts used in the practice of the present invention are made from dried Magnolia plant bark and can be prepared by extracting the bark using an appropriate solvent. Preferred solvents include methanol, ethanol, methylene chloride, hexane, cyclohexane, pentane, petroleum ether, chloroform and ethylene dichloride, one part of plant tissue (dry basis) is extracted with from about 5 to about 50 parts, preferably from about 15 parts to about 30 parts of solvent using an extraction apparatus where the solvent is contacted with the bark to obtain a concentrated paste which is then subjected to one or more additional extraction steps with different solvents to further concentrate the originally obtained paste over an extended period of time, preferably from about 6 hours to about 1-2 days, more preferably for about 1 day.

In one method of extraction, the dried, crushed Magnolia bark in the form of a powder is sequentially contacted with ethanol, methylene chloride, and cyclohexane to form in each step a concentrated paste, the last paste form being dissolved in heated petroleum ether at about 50°-60°C and then dried under vacuum, the final extraction yielding an extract containing about 5 to about 10% by weight honokiol and about 15 to about 25% by weight magnolol.

Magnolol and honokiol are hydroxybiphenyl compounds, the structures of which being represented as follows:



Magnolol



Honokiol

In the practice of the present invention, the antiplaque efficacy of an oral composition containing a noncationic antiplaque agent such as Triclosan, is synergistically enhanced by the presence in the oral composition of an amount of Magnolia Extract which will yield to the oral composition about 0.001 to about 50% by weight of magnolol and preferably about 0.01 to about 0.3 by weight and about 0.02 to about 0.1% by weight of honokiol and preferably about 0.024 to about 20% by weight.

These amounts of magnolol and honokiol are yielded to the oral composition when the Magnolia Extract about 1 to about 20% by weight of magnolol about 2 to about 50% by weight of honokiol.

Typical examples of noncationic halogenated diphenyl ethers which are particularly desirable from considerations of effectiveness, safety and formulation for use in synergistic combination with the Magnolia Extract are 2',4,4' trichloro-2-hydroxy-diphenyl ether (Triclosan) and 2,2'-dihydroxy-5,5'-dibromodiphenyl ether.

The synergistic antiplaque combination of Magnolia Extract and noncationic halogenated diphenyl ether may be administered to the oral cavity while dissolved or suspended in a pharmaceutically acceptable vehicle.

When the noncationic halogenated hydroxyphenyl ether is used in combination with Magnolia Extract to prepare oral compositions such as dentifrices and mouthrinses the

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halogenated hydroxyphenyl ether is incorporated in the oral composition in a non-toxic, effective amount, typically in a range of about 0.003 to about 2%, preferably about 0.02 to about 1% by weight.

5 To further enhance the synergistic antiplaque activity of the Magnolia Extract and halogenated hydrophenyl ether combination of the present invention, an antibacterial enhancing agent may be included in the oral composition. The use of such antibacterial enhancing agents in combination with noncationic antibacterial compounds is known to the art, as for example, US Patent numbers 5,188,821 and 5,192,531.

10 Antibacterial enhancing agents preferred for use in the practice of the present invention include a natural or synthetic anionic polycarboxylates having a molecular weight of about 1,000 to about 5,000,000, preferably about 30,000 to about 500,000. Synthetic anionic polycarboxylates are generally employed in the form of their free acids or preferably partially
15 or more preferably fully neutralized water soluble alkali metal (e.g. potassium and preferably sodium) or ammonium salts. Preferred are 1:4 to 4:1 copolymers of maleic anhydride or acid with another polymerizable ethylenically unsaturated monomer, preferably methyl vinyl
20 either/maleic anhydride having a molecular weight (M.W.) of about 30,000 to about 1,000,000, most preferably about 30,000 to about 500,000. These copolymers are available, for example, under the trade designation Gantrez AN 139 (M.W. 500,000), AN 119 (M.W. 250,000); and preferably Gantrez S-97 Pharmaceutical Grade (M.W. 70,000), of GAF Corporation.

25 Other anionic polycarboxylates useful in the practice of the present invention include the 1:1 copolymers of maleic anhydride with ethyl acrylate, hydroxyethyl methacrylate, N-vinyl-2-pyrrolidone, or ethylene, the latter being available, for example, as Monsanto EMA[®] No: 1103, M.W. 10,000 and Grade 61, and 1:1 copolymers of acrylic acid with methyl or hydroxyethyl methacrylate, methyl or ethyl acrylate, isobutyl methacrylate, isobutyl vinyl ether or N-vinyl-2-pyrrolidone.

30 Additional operative useful polycarboxylate compounds include copolymers of maleic anhydride with styrene, isobutylene or ethyl vinyl ether, polyacrylic, polycationic and polymaleic acids, and sulfonacrylic oligomers of M.W. as low as 1,000 available under the trade designation Uniroyal ND-2.

35 Also useful in the practice of the present invention are the so-called carboxyvinyl polymers, commercially available, for example, under the trade designation Carbopol 934, 940 and 941 from B.F. Goodrich, these polymers consisting of a colloiddally water-soluble polymer

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of polyacrylic acid crosslinked with from about 0.75% to about 2.0% of polyallyl sucrose or polyallyl pentaerythritol as a cross linking agent, often with M.W.'s up to 4-5 million or more.

5 The antibacterial enhancing agent, when employed in the oral composition, is incorporated in the compositions in weight amounts of about 0.05 to about 5%, preferably about 0.1 to about 3%.

10 Fluoride ions may also be included in the oral compositions of the present invention to provide an anticaries effect. Among these materials are inorganic fluoride salts, such as soluble alkali metal fluoride salts, for example, sodium fluoride, potassium fluoride, sodium monofluorophosphate and sodium hexafluorosilicate. Alkali metal and tin fluorides, such as sodium and stannous fluorides, sodium monofluorophosphate and mixtures thereof, are preferred.

15 The amount of fluorine-providing salt is generally present in the oral composition at a concentration of about 0.0005 to about 3.0% by weight. Any suitable minimum amount of such salt may be used, but it is preferable to employ sufficient fluoride salt to release about 300 to 2,000 ppm, more preferably about 800 to about 1,500 ppm, of fluoride ion.

20 The oral composition of the present invention may be a solution of ingredients such as a mouthrinse or it may be a semi-solid such as a toothpaste or gel dentifrice or chewing gum or solid lozenge.

25 In the aspect of this invention wherein the oral composition is a gel or paste, an orally acceptable vehicle, including a water-phase with humectant which is preferably glycerine or sorbitol or an alkylene glycol such as polyethylene glycol or propylene glycol is present, wherein water is present typically in an amount of about 15-40% by weight and glycerine, sorbitol and/or the alkylene glycol (preferably propylene glycol) typically total about 20-75% by weight of the oral composition, more typically about 25-60% by weight.

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When the oral composition is substantially semi-solid or pasty in character, such as a toothpaste or gel, the dentifrice vehicle may contain a dentally acceptable abrasive material such as sodium bicarbonate or water insoluble abrasive material such as sodium metaphosphate, potassium metaphosphate, tricalcium phosphate, dihydrated dicalcium phosphate, anhydrous dicalcium phosphate, calcium pyrophosphate, calcium carbonate, aluminum silicate, hydrated alumina, calcined alumina, silica, bentonite, and mixtures thereof.

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The abrasive material is generally present in the paste or gel composition in weight concentrations of about 10% to about 60% by weight, preferably about 10% to about 30% in a gel and about 25% to about 60% in a paste.

5 Toothpastes as well as gel dentifrices typically contain a natural or synthetic thickener or gelling agent in proportions of about 0.1 to about 10% by weight, preferably about 0.5 to about 5% by weight. Suitable thickeners or gelling agents include Irish moss, iota-carrageenan, kappa-carrageenan, gum tragacanth, starch, polyvinylpyrrolidone, hydroxyethyl propyl
10 cellulose, hydroxybutyl methyl cellulose, hydroxypropyl methyl cellulose, hydroxyethyl cellulose and sodium carboxymethyl cellulose.

In the aspect of the present invention wherein the oral composition is substantially liquid in character such as a mouthwash or rinse, the vehicle is typically a water-alcohol mixture. Generally, the weight ratio of water to alcohol is in the range of from about 3:1 to
15 10:1 and preferably about 4:1 to about 6:1. The alcohol is a non-toxic alcohol such as ethanol or isopropanol. A humectant such as glycerine, sorbitol or an alkylene glycol such as polyethylene glycol or preferably propylene glycol may be present in amount of about 10-30% by weight. Mouthrinses typically contain about 50-85% of water, about 0 to 20% by weight of a non-toxic alcohol and about 10-40% by weight of the humectant .

20 Surfactants are used in the compositions of the present invention to achieve increased prophylactic action and assist in achieving thorough and complete dispersion of Triclosan and Magnolia Extract. The surfactant material is preferably anionic, suitable examples which include water-soluble salts of higher fatty acid monoglyceride monosulfates, such as the
25 sodium salt of the monosulfated monoglyceride of hydrogenated coconut oil fatty acids, higher alkyl sulfates such as sodium lauryl sulfate, alkyl aryl sulfonates such as sodium dodecyl benzene sulfonate, higher alkyl sulfoacetates, higher fatty acid esters of 1,2- dihydroxy propane sulfonate, and the substantially saturated higher aliphatic acyl amides of lower aliphatic amino
30 carboxylic acid compounds, such as those having 12 to 16 carbons in the fatty acid, alkyl or acyl radicals and alkoyl taurines, and the like. Examples of the last mentioned amides and taurates are N-lauroyl sarcosine, and the sodium, potassium and ethanolamine salts of N-lauroyl, N-myristoyl, or N-palmitoyl sarcosine which should be substantially free from soap or similar higher fatty acid material as well as N-methyl-N-cocoyl (or oleoyl or palmitoyl) taurines.

35 Any suitable flavoring or sweetening material may also be employed. Examples of suitable flavoring constituents are flavoring oils, e.g. oil of spearmint, peppermint, wintergreen,

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sassafras, clove, sage, eucalyptus, cinnamon, lemon, and orange, and methyl salicylate. Suitable sweetening agents include sucrose, lactose, maltose, xylitol, sodium cyclamate, perillartine, aspartyl phenyl alanine methyl ester, saccharine and the like. Suitably, flavor and sweetening agents may each or together comprise from about 0.1% to 5% or more of the preparation.

Antitartar agents such as sodium tripolyphosphate, tetrapotassium or tetrasodium pyrophosphate, or mixtures thereof, can be present in the oral compositions of the present invention at concentrations from about 0.5 to about 8% by weight.

Agents used to diminish teeth sensitivity such as potassium chloride, potassium nitrate and potassium citrate can also be included in oral compositions of the present invention at concentrations of about 0.1 to about 10% by weight.

Various other materials may be incorporated in oral compositions of this invention including preservatives, such as sodium benzoate, vitamins and chlorophyll compounds. These adjuvants, when present, are incorporated in the compositions in amounts which do not substantially adversely affect the properties and characteristics desired.

The oral compositions of the present invention may be prepared by suitably mixing the ingredients. For instance, in the preparation of a mouthrinse, the noncationic halogenated hydroxyphenyl ether and hydrogenated lupulone antibacterial agent combination is dispersed in a mixture of ingredients, e.g. alcohol, humectants, surfactants, and flavor are then added and mixed. The ingredients are then mixed under vacuum for about 15-30 minutes. The resulting rinse product is then packaged. Dentifrices are prepared similarly, additional thickener and polishing agents being included in the last or penultimate step.

The antiplaque combination of this invention can be incorporated in lozenges, or in chewing gum or other products, e.g. by stirring into a warm gum base or coating the outer surface of a gum base, illustrative of which may be mentioned include jelutone, rubber latex and vinylite resins desirably with conventional plasticizers or softeners, sugar or other sweeteners or carbohydrates such as glucose, sorbitol and the like.

The vehicle or carrier in a tablet or lozenge is a non-cariogenic solid water-soluble polyhydric alcohol (polyol) such as mannitol, xylitol, sorbitol, malitol, a hydrogenated starch hydrozylate, hydrogenated glucose, hydrogenated disaccharides or hydrogenated polysaccharides, in an amount of about 90 to 98% by weight of the total composition. Salts

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such as sodium bicarbonate, sodium chloride, potassium bicarbonate or potassium chloride may totally or partially replace the polyol carrier. Tableting lubricants, in minor amounts of about 0.1 to 5% by weight, may be incorporated into the tablet or lozenge formulation to facilitate the preparation of both the tablets and lozenges. Suitable lubricants include vegetable oils such as coconut oil, magnesium stearate, aluminum stearate, talc, starch and Carbowax.

Lozenge formulations contain about 2% gum as a barrier agent to provide a shiny surface as opposed to a tablet which has a smooth finish. Suitable non-cariogenic gums include kappa carrageenan, carboxymethyl cellulose, hydroxyethyl cellulose and the like.

The lozenge or tablet may optionally be coated with a coating material such as waxes, shellac, carboxymethyl cellulose, polyethylene/maleic anhydride copolymer or kappa-carrageenan to further increase the time it takes the tablet or lozenge to dissolve in the mouth. The uncoated tablet or lozenge is slow dissolving, providing a sustained release rate of active ingredients of about 3 to 5 minutes. Accordingly, the solid dose tablet and lozenge composition of this invention affords a relatively longer time period of contact of the teeth in the oral cavity with the active ingredients.

The following Examples further illustrate the present invention, but it is understood that the invention is not limited thereto. All amounts and proportions referred to herein and in the appended claims are by weight unless otherwise indicated.

Example I

A 0.3% solution in ethanol of Magnolia Extract containing 8% by weight honokiol and 21% by weight magnolol and a 0.3% by weight solution in ethanol of Triclosan were prepared, and the mixed solution at a 1:1 weight ratio designated "Composition 1" was evaluated in an MIC assay for bactericidal activity against *S. mutans* and *F. nuceatum*. The bacterial strain *F. nuceatum* is implicated in the occurrence of gingivitis.

MIC ASSAY

The bacterial strains of *S. Mutans* and *F. nuceatum* grown for 24 hours in trypticase soy broth and FTG* broth for 48hours at 37°C respectively to adjust its optical density between 0.1 and 0.2 absorption units at 610 nm prior to MIC determinations.

* FTG - Fluid Thioglycolate

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The Magnolia Extract and Triclosan solution mixture (Composition 1) was diluted and MIC assayed using the microtiter format according to standard procedures (Manual of Clinical Microbiology, 1995). The results are recorded in Table I below.

The FIC value (fractional inhibitory concentration) of Composition 1 was determined to assess whether the antibacterial efficacy of the Magnolia Extract Triclosan combination exhibited synergistic activity as is described in L.B. Quesnel et al in Journal of Applied Bacteriology, 1978, vol. 45, pages 397-405, L.O. Garrod et al in Antibiotic and Chemotherapy, pages 282-286 and 514-518.

$$\text{FIC} = \frac{\text{MIC of Triclosan in mixture}}{\text{MIC of Triclosan alone}} + \frac{\text{MIC of Magnolia Extract in mixture}}{\text{MIC of Magnolia Extract alone}}$$

FIC	Implies
≤ 0.7	Synergism
1 ± 0.3	Additive
≥ 1.3	Antagonistic

The FIC value for the Magnolia Extract/Triclosan combination is recorded in Table I.

For purposes of comparison, individual 1% by weight solutions of Magnolia Extract, (designated "Composition C1") and Triclosan, (designated "Composition 2") were also subjected to MIC assay. The results are also recorded in Table I below.

TABLE I			
Composition No.	Solution	S. mutans	F. nucleatum
▪ C1	Magnolia Extract	62.5 ± 0.0	31.3 ± 0.0
▪ C2	Triclosan	15.6 ± 0.0	2.0 ± 0.0
▪ 1	Magnolia Extract + Triclosan	7.8 ± 0.0	1.3 ± 0.6
	FIC Composition 1	0.62	0.69

The results recorded in Table I show that Composition 1, the combination of the Magnolia Extract and Triclosan exhibit significantly greater bactericidal activity against S. mutans and F. nucleatum than would be expected from the additive effect of these materials. The FIC value for Composition 1 indicates an unexpected synergistic antibacterial activity against S. mutans and F. nucleatum.

Example II

A dentifrice formulation (designated "Composition A") containing both Triclosan and a Magnolia Extract containing 8% by weight honokiol and 21% by weight manganol and the

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ingredients listed in Table II was prepared. A dentifrice having substantially same ingredients as Composition A except that the Magnolia Extract was not included in the dentifrice was used as a comparative composition and designated "Composition B". The ingredients of Compositions A and B are recorded in Table II below.

5

TABLE II		
Composition Ingredients	A Weight %	B Weight %
Di water	16.107	15.807
Glycerin	20.00	20.00
Carboxymethyl cellulose	1.100	1.100
Carrageenan	0.400	0.400
Sodium saccharin	0.300	0.300
Sodium fluoride	0.243	0.243
Titanium dioxide	0.500	0.500
Noncrystalizing sorbitol	20.850	20.850
Gantrez S-97	15.000	15.000
Silica abrasive	20.000	20.000
Silica thickener	1.500	1.500
Flavor	1.000	1.000
Sodium hydroxide - 50% solution	1.200	1.200
Triclosan	0.300	0.300
Magnolia Extract	0	0.300
SLS	1.500	1.500
TOTAL	100.000	100.000

10 In a six week study to monitor the effect of Composition A and comparative Composition B on gingivitis, 40 subjects were randomly assigned to one of two treatment groups, one group of subjects brushed their teeth twice daily with Composition A and the second group with Composition B. Product efficacy was clinically assessed using standard scoring methods. All subjects were examined professionally at baseline, three and six week intervals for presence of gingivitis according to the Gingival Index system (GI, Loe 1967).

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The scoring criteria was as follows:

Gingivital inflammation

- 5 **Score 0** Absence of inflammation
 Score 1 Mild inflammation – slight change in color and little change in texture
 Score 2 Moderate inflammation – moderate glazing, redness, edema and hypertrophy-
 bleeding on probing
 10 **Score 3** Severe inflammation - marked redness and hypertrophy; tendency to
 spontaneous bleeding

The GI score results are recorded in Table III as average/tooth/subject score.

TABLE III						
Gingival Index Scores						
Dentifrices	N	Elapsed Time			%Reduction v. Baseline	P
		Baseline	3 Weeks	6 Weeks		
Composition A	20	1.09	0.02	0.04	95%	P=0.002
Composition B	20	1.11	0.67	0.58	47%	

- 15 The results recorded in Table III indicate that the presence of the Magnolia Extract in the dentifrice composition produced a significant reduction in gingivitis by those subjects who brushed their teeth with Composition A.

CLAIMS

5 What is claimed is:

1. An oral antigingivitis composition comprising an orally acceptable vehicle and an effective antiplaque amount of a combination of a noncationic halogenated hydroxydiphenyl ether and a an extract of Magnolia Cortex , the bark of Magnolia officinalis containing hydroxybiphenol compounds.
10
2. The composition of claim 1 wherein nonionic halogenated diphenyl ether is present in the oral composition in an amount in the range of about 0.003 to about 2.0% by weight.
- 15 3. The composition of claim 1 wherein the nonionic halogenated diphenyl ether compound is Triclosan.
4. The composition of claim 1 wherein the hydroxybiphenyl compounds are selected from magnolol, honokiol and mixtures thereof.
20
5. The composition of claim 1 wherein the Magnolia extract contains 1 to 20% by weight honokiol and 2 to 50% by weight magnolol.
- 25 6. The composition of claim 1 wherein the Magnolia extract is present in the composition in an amount in the range of about 0.001 to about 10% by weight.
7. The composition of claim 1 wherein there is present in the composition a synthetic anionic polycarboxylate.
- 30 8. The composition of claim 7 wherein the polycarboxylate is a methyl vinyl ether/maleic anhydride copolymer.
9. A method of inhibiting the growth of plaque bacteria by contacting the bacteria with a composition comprising a pharmaceutically acceptable vehicle and an effective antiplaque
35 amount of a combination of a noncationic halogenated hydroxydiphenyl ether and a Magnolia Extract containing hydroxybiphenyl compounds.

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10. The method of claim 9 wherein nonionic halogenated diphenyl ether is present in the composition in an amount in the range of about 0.003 to about 2.0% by weight.

5 11. The method of claim 9 wherein the nonionic halogenated diphenyl ether compound present in the composition is Triclosan.

12. The method of claim 9 wherein the hydroxybiphenyl compounds of the Magnolia extract present in the composition are selected from magnolol, honokiol and mixtures thereof.

10 13. The method of claim 9 wherein the Magnolia extract present in the composition contains 1 to 20% by weight honokiol and about 2 to about 50% by weight magnolol.

14. The composition of claim 1 wherein the Magnolia extract is present in the composition in an amount in the range of about 0.001 to about 10% by weight.

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15. The method of claim 9 wherein there is present in the composition a synthetic anionic polycarboxylate.

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16. The composition of claim 15 wherein the polycarboxylate is a methyl vinyl ether/maleic anhydride copolymer.

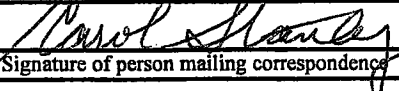
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I. Certification under 37 CFR 1.10 (if applicable)

EL424780837US
Express Mail mailing number

09 May 2001
Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Assistant Commissioner for Patents, Washington, D.C. 20231.


Signature of person mailing correspondence

Carol Stanley
Typed or printed name of person mailing correspondence

II. ☒ New International Application

TITLE	SYNERGISTIC ANTIPLAQUE/ANTIGINGIVITIS ORAL COMPOSITION
-------	--

Earliest priority date (Day/Month/Year)
10 May 2000

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

- A. ☐ The invention disclosed was **not** made in the United States.
- B. ☐ There is no prior U.S. application relating to this invention.
- C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. (NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority).

application no.	USSN 09/568,114	filed on	10 May 2000
application no.		filed on	

- D. ☐ The present international application ☐ is identical ☐ contains less subject matter than that found in the prior U.S. application(s) identified in paragraph C.
- E. ☐ The present international application ☐ contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages and ☐ DOES NOT ALTER ☐ MIGHT BE CONSIDERED TO ALTER the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15

III. ☐ A Response to an Invitation from the RO/US. The following document(s) is (are) enclosed:

- A. ☐ A Request for An Extension of Time to File a Response
- B. ☐ A Power of Attorney (General or Regular)
- C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

- D. ☐ Submission of Priority Documents

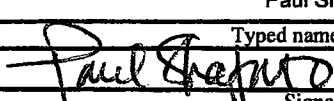
Priority document		Priority document	
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- E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT 91 ☐ A Petition ☐ A Sequence Listing Diskette

V. ☐ Other (please specify):

The person signing this form is the:

☐ Applicant	Paul Shapiro
☒ Attorney/Agent (Reg. No.) 22,322	Typed name of signer
☐ Common Representative	 Signature

PCT REQUEST

Original (for SUBMISSION) - printed on 09.05.2001 11:23:36 AM

6477-00

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	6477-00
I	Title of invention	SYNERGISTIC ANTIPLAQUE/ANTIGINGIVITIS ORAL COMPOSITION
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States
II-4	Name	COLGATE-PALMOLIVE COMPANY
II-5	Address:	300 Park Avenue New York, NY 10022 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	732-878-7547
II-9	Facsimile No.	732-878-7853
III-1	Applicant and/or inventor	
III-1-1	This person is:	inventor only
III-1-4	Name (LAST, First)	SCHERL, Dale, S.
III-1-5	Address:	3056 Gloucester Drive Bethlehem, PA 18020 United States of America
III-2	Applicant and/or inventor	
III-2-1	This person is:	inventor only
III-2-4	Name (LAST, First)	HERLES, Susan, M.
III-2-5	Address:	139 Old Clinton Road Flemington, NJ 08822 United States of America

PCT REQUEST

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6477-00

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23

III-3	Applicant and/or inventor	
III-3-1	This person is:	inventor only
III-3-4	Name (LAST, First)	XU, Tao
III-3-5	Address:	160 Pine Street Newton, MA 02466 United States of America
III-4	Applicant and/or inventor	
III-4-1	This person is:	inventor only
III-4-4	Name (LAST, First)	GAFFAR, Abdul
III-4-5	Address:	89 Carter Road Princeton, NJ 08540 United States of America
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	
IV-1-1	Name (LAST, First)	SHAPIRO, Paul
IV-1-2	Address:	Colgate-Palmolive Company 909 River Road P.O. Box 1343 Piscataway, NJ 08855-1343 United States of America
IV-1-3	Telephone No.	732-878-7547
IV-1-4	Facsimile No.	732-878-7853
IV-1-5	e-mail	paul_shapiro@colpal.com
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT

PCT REQUEST

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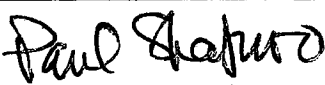
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW	
V-3	National Patent (States which have become party to the PCT after the issuance of this version of EASY)	CO Colombia EC Ecuador	
V-5	Precautionary Designation Statement In addition to the designations made under Items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	10 May 2000 (10.05.2000)	
VI-1-2	Number	09/568,114	
VI-1-3	Country	US	
VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	4	-
VIII-2	Description	12	-
VIII-3	Claims	2	-
VIII-4	Abstract	1	EZABST00.TXT
VIII-5	Drawings	0	-
VIII-7	TOTAL	19	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract		
VIII-19	Language of filing of the international application	English	

PCT REQUEST

4/4

6477-00

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IX-1	Signature of applicant or agent	
IX-1-1	Name (LAST, First)	SHAPIRO, Paul

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PCT (ANNEX - FEE CALCULATION SHEET)Original (for **SUBMISSION**) - printed on 09.05.2001 11:23:36 AM

6477-00

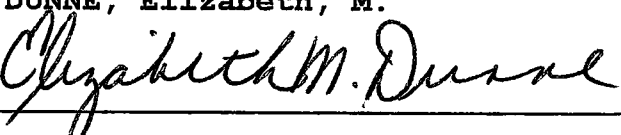
(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex)			
0-4-1	PCT Fee Calculation Sheet Prepared using	PCT-EASY Version 2.91 (updated 01.01.2001)		
0-9	Applicant's or agent's file reference	6477-00		
2	Applicant	COLGATE-PALMOLIVE COMPANY		
12	Calculation of prescribed fees	fee amount/multiplier	total amounts (USD)	
12-1	Transmittal fee T	⇒	240	
12-2	Search fee S	⇒	846	
12-3	International fee			
	Basic fee			
	(first 30 sheets) b1	382		
12-4	Remaining sheets	0		
12-5	Additional amount (X)	9		
12-6	Total additional amount b2	0		
12-7	b1 + b2 = B	382		
12-8	Designation fees			
	Number of designations contained in international application	88		
12-9	Number of designation fees payable (maximum 6)	6		
12-10	Amount of designation fee (X)	82		
12-11	Total designation fees D	492		
12-12	PCT-EASY fee reduction R	-117		
12-13	Total International fee (B+D-R) I	⇒	757	
12-14	Fee for priority document			
	Number of priority documents requested	1		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇒	15	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇒	1,858	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions			
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	is hereby authorized to charge the total fees indicated above to my deposit account	✓		

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 09.05.2001 11:23:36 AM

6477-00

12-20-2	is hereby authorized to charge any deficiency or credit any over-payment in the total fees indicated above to my deposit account	✓
12-20-3	is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account	✓
12-21	Deposit account No.	03-2457
12-22	Date	09 May 2001 (09.05.2001)
12-23	Name and signature	DUNNE, Elizabeth, M. 

VALIDATION LOG AND REMARKS

13-2-2	Validation messages States	Green? More designations could be made. The following States have not been designated: US. Please verify.
		Yellow! Additional national designation added: Obtain updated maintenance tables rather than using this field.
13-2-6	Validation messages Contents	Yellow! The power of attorney or a copy of the general power of attorney will need to be furnished unless all applicants sign the request form.
		Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

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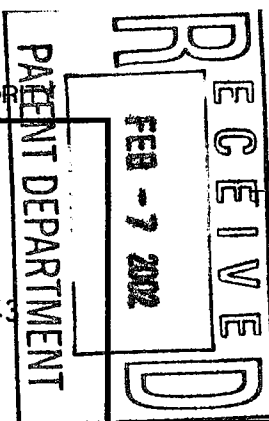
From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:
COLGATE-PALMOLIVE COMPANY
Attn. Shapiro, Paul
909 River Road
P.O. Box 1343
Piscataway, New Jersey 08855-1343
UNITED STATES OF AMERICA



Date of mailing (day/month/year) 01/02/2002	
Applicant's or agent's file reference 6477-00	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US 01/ 14956	International filing date (day/month/year) 09/05/2001
Applicant COLGATE-PALMOLIVE COMPANY	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chantal Meyer

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 6477-00	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 01/ 14956	International filing date (day/month/year) 09/05/2001	(Earliest) Priority Date (day/month/year) 10/05/2000
Applicant COLGATE-PALMOLIVE COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K7/16 A61K7/26 A61K35/78 A61K31/085		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, MEDLINE, CHEM ABS Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 35599 A (DAEWOONG PHARMACEUTICAL CO.LTD. ET AL.) 2 October 1997 (1997-10-02) page 3, line 24 -page 4, line 4 page 23, line 4 - line 21 page 21, line 17 - line 22 claims 1-7; examples 2-4 ---	1,9
A	PATENT ABSTRACTS OF JAPAN vol. 6, no. 169 (C-122), 2 September 1982 (1982-09-02) & JP 57 085319 A (TSURUI YAKUHIIN KOGYO KK), 28 May 1982 (1982-05-28) abstract --- -/--	1,4,9,12
☒ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
° Special categories of cited documents :		
A document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 22 January 2002		Date of mailing of the international search report 01/02/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Alvarez Alvarez, C

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PUBLICATION NUMBER : 57085319
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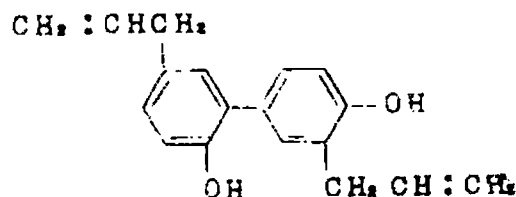
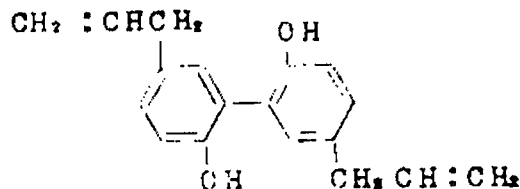
APPLICATION DATE : 16-11-80
APPLICATION NUMBER : 55161091

APPLICANT : TSURUI YAKUHHIN KOGYO KK;

INVENTOR : KYOZUKA MASAGO;

INT.CL. : A61K 35/00 A61K 35/78 //(A61K 35/78
, A61K 31/05)

TITLE : AGENT FOR DENTAL CARIES



ABSTRACT : PURPOSE: To provide an agent for preventing or inhibiting the progress of dental caries and containing the extract of KOBOKU (bark of *Magnolia officinalis* REHD. et WILS.), OREN (rhizome of *Coptis chinensis* FRANCH.) etc. or magnolol and honokiol which are the active components of the above extract.

CONSTITUTION: The objective agent contains the extract of KOBOKU, OREN, GOBAISHI (gall of *Rhus chinensis* MILL), GENNOSHOKO (whole grass of *Geranium thunbergii* SIEB. et ZUCC.), OBAKU (bark of *Phellodendron amurense* RUPR.), etc. and/or their active components (e.g. magnolol or formula I, honokiol of formula II, berberine, etc.). The agent inhibits remarkably the growth of *Streptomyces mutans* which is a cariogenic bacterium having the strongest cariogenicity. The agent has somewhat milder activity than erythromycin, and lower side effects than antibiotic substances, and is suitable for administration for a long period. It also exhibits remarkable effect at a low concentration in a short time. Administered directly in the oral cavity, or by mixing with tooth paste, or in the form of troche or sublingual tablet.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 188 821 A (ABDUL GAFFAR ET AL.) 23 February 1993 (1993-02-23) cited in the application examples 1,2 claims 1-5,10-12,16-20 -----	1,3,7-9, 11,15,16

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Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9735599	A	02-10-1997	KR	176015 B1	20-03-1999
			AU	2180097 A	17-10-1997
			WO	9735599 A1	02-10-1997
JP 57085319	A	28-05-1982	JP	1038084 B	11-08-1989
			JP	1556516 C	23-04-1990
US 5188821	A	23-02-1993	US	4894220 A	16-01-1990
			US	5043154 A	27-08-1991
			AT	398034 B	25-08-1994
			AT	296789 A	15-01-1994
			AT	397765 B	27-06-1994
			AT	296889 A	15-11-1993
			AU	632776 B2	14-01-1993
			AU	4676889 A	05-07-1990
			AU	625379 B2	09-07-1992
			AU	4676989 A	05-07-1990
			AU	637777 B2	10-06-1993
			AU	4677189 A	28-02-1991
			BE	1004366 A5	10-11-1992
			BE	1006029 A5	26-04-1994
			BE	1005904 A5	08-03-1994
			BE	1007179 A4	18-04-1995
			BR	8906850 A	02-10-1990
			BR	8906866 A	09-10-1990
			CA	2006707 A1	25-02-1991
			CA	2006713 A1	29-06-1990
			CA	2006717 A1	29-06-1990
			CH	679674 A5	31-03-1992
			CH	679741 A5	15-04-1992
			CH	679639 A5	31-03-1992
			CN	1044047 A , B	25-07-1990
			CZ	8907510 A3	11-08-1999
			CZ	8907511 A3	14-02-1996
			CZ	8907512 A3	13-08-1997
			DE	3942641 A1	28-02-1991
			DE	3942642 A1	30-08-1990
			DE	3942643 A1	05-07-1990
			DK	670989 A	30-06-1990
			DK	671089 A	30-06-1990
			DK	671189 A	26-02-1991
			EG	19073 A	30-06-1994
			EG	19074 A	31-03-1996
			ES	2023294 A6	01-01-1992
			ES	2023296 A6	01-01-1992
			FI	100691 B1	13-02-1998
			FI	98121 B	15-01-1997
			FI	946119 A	28-12-1994
			FR	2651235 A1	01-03-1991
			FR	2641186 A1	06-07-1990
			FR	2641187 A1	06-07-1990
			FR	2681529 A1	26-03-1993
			FR	2684550 A1	11-06-1993
			GB	2227660 A , B	08-08-1990
			GB	2235201 A , B	27-02-1991
			GB	2227661 A , B	08-08-1990
			GB	2257362 A , B	13-01-1993

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, Gaijeong-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 With international search report.	

(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.

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