

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-063480- -00003-0000

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AS. 104.418

Señores

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIVISION DE NUEVAS CREACIONES**

E. S. D.

REF.: Expediente No. 07 063.480 - Solicitud de Patente FASE NACIONAL

Corresp. a la Solicitud Internacional PCT/US2005/046522.

a nombre de: **COLGATE-PALMOLIVE COMPANY.**

Titulada: COMPOSICIONES PARA EL CUIDADO ORAL QUE CONTIENEN  
FLAVONOIDES Y FLAVANOS.

JUAN PABLO CADENA SARMIENTO, vecino de Bogotá, portador de la tarjeta profesional No. 57492 del Consejo Superior de la Judicatura, obrando como apoderado de la Sociedad **COLGATE-PALMOLIVE COMPANY**, según lo acredita el documento de poder presentado en esa División, de acuerdo con el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito solicitar que se examine si la invención contenida en la solicitud en referencia es patentable.

De acuerdo con lo anterior, me permito anexar el recibo oficial de caja No. 08-44,635 por valor de \$420.000.

De la Señora Jefe atentamente,

**JUAN PABLO CADENA SARMIENTO**

C.C. No. 80.410.337 de Usaquén

T.P. No. 57492 del C.S.J.

Cra 7 No. 71-21 Torre B, Piso 4

Bogotá, 10 de julio de 2008

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Act. 538 PETICION

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Act: 538 PETICION Folios: 2

RECIBO OFICIAL DE OCAF : 08 - 44/02  
FECHA : JUNIO 5 DE 2008

Area de Control de Calidad

| REQUISITANTE                 | TIPO PAGO    | BANCO           | CUENTA    | Nº. PASO | FECHA POC  | V. PAGO       |
|------------------------------|--------------|-----------------|-----------|----------|------------|---------------|
| PRIMERO A CONTROL DE CALIDAD | CONSIGNACION | BANCO DE BOGOTÁ | 162754087 | 125576   | 04/06/2008 | 15,111,000.00 |

Area de Control de Calidad

| CANT. ENTREGADA | CONCEPTO | TOTAL CONCEPTO |
|-----------------|----------|----------------|
|-----------------|----------|----------------|

|   |                         |    |                                   |            |
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RESPONSABLE :

RECIBO DE OCAF APLICADO AL EXPEDIENTE DE :

**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. 07-63480

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

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.

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US 20030216481A1

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(19) **United States**(12) **Patent Application Publication** (10) Pub. No.: **US 2003/0216481 A1**  
(43) Pub. Date: **Nov. 20, 2003**(54) **FORMULATION OF A MIXTURE OF  
FREE-B-RING FLAVONOIDS AND FLAVANS  
AS A THERAPEUTIC AGENT**

(52) U.S. Cl. 514.732

(75) Inventor: **Qi Jia, Superior, CO (US)**(57) **ABSTRACT**

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(73) Assignee: **UNIGEN PHARMACEUTICALS,  
INC., Broomfield, CO**(21) Appl. No.: **10:427,746**(22) Filed: **Apr. 30, 2003****Related U.S. Application Data**(60) Provisional application No. 60/377,168, filed on Apr.  
30, 2002.**Publication Classification**(51) Int. Cl. **A61K 31/05, A01N 31/08**

The present invention provides a novel composition of matter comprised of a mixture of two specific classes of compounds—Free-B-ring flavonoids and flavans—for use in the prevention and treatment of diseases and conditions mediated by the COX-2 and 5-LO pathways. The present invention further provides a novel method for simultaneously inhibiting the cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO) enzymes, and reducing cox-2 mRNA production. Finally, the present invention includes a method for weight loss and blood glucose control. The methods of this invention are comprised of administering to a host in need thereof an effective amount of the composition of this invention together with a pharmaceutically acceptable carrier. This invention relates generally to the prevention and treatment of diseases and conditions mediated by the cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LO) pathways, including but not limited to the relief joint discomfort and pain associated with conditions such as osteoarthritis, rheumatoid arthritis, and other injuries that result from overuse.

and 5-LO mediated diseases and conditions, including, but are not limited to osteoarthritis, rheumatoid arthritis, menstrual cramps, arteriosclerosis, heart attack, obesity, diabetes, syndrome X, Alzheimer's disease, respiratory allergic reaction, chronic venous insufficiency, hemorrhoids, Systemic Lupus Erythematosus, psoriasis, chronic tension headache, migraine headaches, inflammatory bowel disease, topical infections caused by virus, bacteria, fungus, sunburn, thermal burns, contact dermatitis, melanoma and carcinoma. Finally, Univestin™ m has been found in human clinical study that it can cause weight loss and reduce blood glucose level due to improvement of flexibility, mobility and increase physical activity.

[0156] The present invention is also directed toward therapeutic compositions comprising the therapeutic agents of the present invention. The therapeutic agents of the instant invention can be administered by any suitable means, including, for example, parenteral, topical, oral or local administration, such as intradermally, by injection, or by aerosol. The particular mode of administration will depend on the condition to be treated. It is contemplated that administration of the agents of the present invention may be via any bodily fluid, or any target or any tissue accessible through a body fluid. In the preferred embodiment of the invention, the agent is administered by injection. Such injection can be locally administered to any affected area. A therapeutic composition can be administered in a variety of unit dosage forms depending upon the method of administration. For example, unit dosage forms suitable for oral administration of an animal include powder, tablets, pills and capsules. Preferred delivery methods for a therapeutic composition of the present invention include intravenous administration and local administration by, for example, injection or topical administration. A therapeutic reagent of the present invention can be administered to any animal, preferably to mammals, and more preferably to humans.

[0157] For particular modes of delivery, a therapeutic composition of the present invention can be formulated so as to include other components such as a pharmaceutically acceptable excipient, an adjuvant, and/or a carrier. For example, compositions of the present invention can be formulated in an excipient that the animal to be treated can tolerate. Examples of such excipients include but are not limited to cellulose, silicon dioxide, dextrates, sucrose, sodium starch glycolate, calcium phosphate, calcium sulfate, water, saline, Ringer's solution, dextrose solution, mannitol, Hank's solution, and other aqueous physiologically balanced salt solutions. Nonaqueous vehicles, such as fixed oils, sesame oil, ethyl oleate, or triglycerides may also be used. Other useful formulations include suspensions containing viscosity-enhancing agents, such as sodium carboxymethylcellulose, sorbitol, or dextran. Excipients can also contain minor amounts of additives, such as substances that enhance isotonicity and chemical stability. Examples of buffers include phosphate buffer, bicarbonate buffer, Tris buffer, histidine, citrate, and glycine, or mixtures thereof, while examples of preservatives include thimerosal, m- or o-cresol, formalin and benzyl alcohol. Standard formulations can either be liquid injectables or solids, which can be taken up in a suitable liquid as a suspension or solution for injection. Thus, in a non-liquid formulation, the excipient can comprise dextrose, human serum albumin, preservatives, etc., to which sterile water or saline can be added prior to administration.

[0158] In one embodiment of the present invention, the composition can also include an adjuvant or a carrier. Adjuvants are typically substances that generally enhance the function of the formula in preventing and treating indications related to COX & LO pathways. Suitable adjuvants include, but are not limited to, Freund's adjuvant; other bacterial cell wall components; aluminum-based salts; calcium-based salts; silica; boron; histidine, glucosamine sulfates, Chondroitin sulfate, copper gluconate, polynucleotides; vitamin D, vitamin K, toxoids; shark and bovine cartilage; serum proteins; viral coat proteins; other bacterial-derived preparations; gamma interferon; block copolymer adjuvants, such as Hunter's Titermax adjuvant (Vaxcel, T.M., Inc. Norcross, Ga.); Ribi adjuvants (available from Ribi ImmunoChem Research, Inc., Hamilton, Mont.); and saponins and their derivatives, such as Quil A (available from Superfos Biosector A/S, Denmark). Carriers are typically compounds that increase the half-life of a therapeutic composition in the treated animal. Suitable carriers include, but are not limited to, polymeric controlled release formulations, biodegradable implants, liposomes, bacteria, viruses, oils, esters, and glycols.

[0159] One embodiment of the present invention is a controlled release formulation that is capable of slowly releasing a composition of the present invention into an animal. As used herein, a controlled release formulation comprises a composition of the present invention in a controlled release vehicle. Suitable controlled release vehicles include, but are not limited to, biocompatible polymers, other polymeric matrices, capsules, microcapsules, micro-particles, bolus preparations, osmotic pumps, diffusion devices, liposomes, lipospheres, and transdermal delivery systems. Other controlled release formulations of the present invention include liquids that, upon administration to an animal, form a solid or a gel in situ. Preferred controlled release formulations are biodegradable (i.e., bio-erodable).

[0160] Once the therapeutic composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or dehydrated or lyophilized powder; or directly encapsulated and/or tableted with other inert carriers for oral administration. Such formulations may be stored either in a ready to use form or requiring reconstitution immediately prior to administration. The manner of administering formulations containing the compositions for systemic delivery may be via oral, subcutaneous, intramuscular, intravenous, intranasal or vaginal or rectal suppository.

[0161] The amount of the composition that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, which can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness or advancement of the disease or condition, and should be decided according to the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. For example, an effective amount of the composition can readily be determined by administering graded doses of the composition and observing the desired effect.

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With reference to Table 5,  $IC_{50}$  values are generally lower for COX-1 than COX-2. Additionally, whole blood was also measured for the differential inhibition of  $PGE_2$  generation (a measure of COX-2 in this system) or thromboxane B2 (TXB<sub>2</sub>) (a measure of COX-1 activation). Referring to Table 7, these studies clearly demonstrate specificity for COX-2 inhibition within the assays based on whole blood cells. However, studies using the THP-1 and HOSC-based model system actually showed greater selectivity for COX-1. Possible reasons for this discrepancy are the fundamental differences between immortalized cell lines that constitutively express each of the enzymes and primary cells derived from whole blood that are induced to express COX enzymes. Primary cells are a more relevant model to study inflammation in vivo. Additionally, the compounds used to identify COX-1 vs. COX-2 activity vary in each of these systems and consequently are not directly comparable.

TABLE 7

| Plant Source of the               | Cell Line Based Assay |                 | Whole Blood Assay |                 |
|-----------------------------------|-----------------------|-----------------|-------------------|-----------------|
|                                   | $IC_{50}$ COX-2       | $IC_{50}$ COX-1 | $IC_{50}$ COX-2   | $IC_{50}$ COX-1 |
| Organic extracts                  |                       |                 |                   |                 |
| <i>A. catechu</i>                 | 78 $\mu$ g/mL         | 12 $\mu$ g/mL   | 47 $\mu$ g/mL     | >50 $\mu$ g/mL  |
| <i>S. orthocalyx</i> (root)       | 57 $\mu$ g/mL         | 6 $\mu$ g/mL    | 17 $\mu$ g/mL     | >50 $\mu$ g/mL  |
| <i>S. balanifera</i>              | 82 $\mu$ g/mL         | 4 $\mu$ g/mL    | 2 $\mu$ g/mL      | 8 $\mu$ g/mL    |
| <i>S. latifolia</i> (whole plant) | 87 $\mu$ g/mL         | 37 $\mu$ g/mL   | 8 $\mu$ g/mL      | 20 $\mu$ g/mL   |

Example 11

[0200] Inhibition of 5-Lipoxygenase by the Catechin from *Acacia catechu*

[0201] As noted above, one of the most important pathways involved in the inflammatory response is produced by non-heme, iron-containing, lipoxygenases (5-LO, 12-LO, and 15-LO), which catalyze the addition of molecular oxygen onto fatty acids such as AA (AA) to produce the hydroperoxides 5-, 12- and 15-HPETE, which are then converted to leukotrienes. There were early indications that the flavan extract from *A. catechu* may provide some degree of 5-LO inhibition, thereby preventing the formation of 5-HPETE. A Lipoxygenase Inhibitor Screening Assay Kit (Cayman Chemical, Inc., Cat #760700) was used to assess whether the purified flavan catechin from *Acacia catechu* directly inhibited 5-LO in vitro. The 15-LO from soybeans normally used in the kit was replaced with potato 5-LO, after a buffer change from phosphate to a tris-based buffer using microfiltration was performed. This assay detects the formation of hydroperoxides through an oxygen sensing chromagen. Briefly, the assay was performed in triplicate by adding 90  $\mu$ L of 0.17 units  $\mu$ L potato 5-LO, 20  $\mu$ L of 1.1 mM AA, 100  $\mu$ L of oxygen-sensing chromagen, and 10  $\mu$ L of purified flavan inhibitor to final concentrations ranging from 0 to 500  $\mu$ g/mL. The  $IC_{50}$  for 5-LO inhibition from catechin was determined to be 1.38  $\mu$ g/mL unit of enzyme.

Example 12

[0202] Preparation of a Standardized Extract from *Acacia catechu*

[0203] *Acacia catechu* (500 mg of ground bark) was extracted with the following solvent systems: (1) 100% water, (2) 80:20 water:methanol, (3) 60:40 water:methanol, (4) 40:60 water:methanol, (5) 20:80 water:methanol, (6) 100% methanol, (7) 80:20 methanol:THF, (8) 60:40 methanol:THF. The extracts were concentrated and dried under low vacuum.

[0204] The identification of the chemical components in each extract was achieved by HPLC using a PhotoDiode Array detector (HPLC PDA) and a 250 mmx4.6 mm C18 column. The chemical components were quantified based on retention time and PDA data using catechin and epicatechin as standards. The results are set forth in Table 8 and FIG. 9.

[0205] As shown in Table 6, the flavan extract generated from solvent extraction with 80% methanol-water provided the best concentration of flavan components.

TABLE 8

| Solvents for Generating Standardized Flavan Extracts from <i>Acacia catechu</i> |                   |                            |                           |                        |
|---------------------------------------------------------------------------------|-------------------|----------------------------|---------------------------|------------------------|
| Extraction Solvent                                                              | Weight of Extract | % Extractable from BioMass | Total amount of Catechins | % Catechins in Extract |
| 100% water                                                                      | 262.8 mg          | 56.56%                     | 13 mg                     | 12.02%                 |
| water:methanol (80:20)                                                          | 282.9 mg          | 56.58%                     | 15 mg                     | 11.19%                 |
| water:methanol (60:40)                                                          | 287.6 mg          | 57.52%                     | 15 mg                     | 13.54%                 |
| water:methanol (40:60)                                                          | 294.4 mg          | 52.05%                     | 19 mg                     | 13.77%                 |
| water:methanol (20:80)                                                          | 221.8 mg          | 44.55%                     | 15 mg                     | 14.83%                 |
| 100% methanol                                                                   | 215.7 mg          | 43.11%                     | 15 mg                     | 12.73%                 |
| methanol:THF (80:20)                                                            | 294.4 mg          | 52.05%                     | 11 mg                     | 8.81%                  |
| methanol:THF (60:40)                                                            | 287.6 mg          | 57.52%                     | 15 mg                     | 13.54%                 |

Example 13

[0206] Preparation of Standardized Free-B-ring Flavonoid Extracts from Various Scutellaria Species

[0207] *Scutellaria orthocalyx* (500 mg of ground root) was extracted twice with 25 mL of the following solvent systems: (1) 100% water, (2) 80:20 water:methanol, (3) 60:40 water:methanol, (4) 40:60 water:methanol, (5) 20:80 water:methanol, (6) 100% methanol, (7) 80:20 methanol:THF, (8) 60:40 methanol:THF. The extracts were combined, concentrated and dried under low vacuum. Identification of chemical components in each extract was performed by HPLC using a PhotoDiode Array detector (HPLC PDA) and a 250 mmx4.6 mm C18 column. The chemical components were quantified based on retention time and PDA data using baicalin, baicalin, scutellarin, and wogonin as standards. The results are set forth in Table 9.

TABLE 9

| Quantification of Free-B-ring Flavonoids Extracted from<br><i>Scutellaria orthogalys</i> |                         |                                     |                                     |                            |
|------------------------------------------------------------------------------------------|-------------------------|-------------------------------------|-------------------------------------|----------------------------|
| Extraction<br>Solvent                                                                    | Weight<br>of<br>Extract | %<br>Extractable<br>from<br>BioMass | Total<br>amount<br>of<br>Flavonoids | % Flavonoids<br>in Extract |
| 100% water                                                                               | 10 mg                   | 16.2%                               | 1.62 mg                             | 0.20%                      |
| Water:methanol<br>(30:70)                                                                | 138.5 mg                | 27.7%                               | 3.88 mg                             | 0.88%                      |
| Water:methanol<br>(60:40)                                                                | 179.5 mg                | 33.9%                               | 6.05 mg                             | 8.40%                      |
| Water:methanol<br>(40:60)                                                                | 142.2 mg                | 28.4%                               | 4.04 mg                             | 11.26%                     |
| Water:methanol<br>(20:80)                                                                | 104.5 mg                | 20.0%                               | 2.04 mg                             | 7.00%                      |
| 100% methanol                                                                            | 57.5 mg                 | 11.5%                               | 0.69 mg                             | 10.42%                     |
| methanol:THF<br>(50:50)                                                                  | 79.5 mg                 | 11.9%                               | 1.85 mg                             | 8.76%                      |
| methanol:THF<br>(30:70)                                                                  | 58.8 mg                 | 11.8%                               | 1.10 mg                             | 10.71%                     |

[0208] *Scutellaria baicalensis* (1000 mg of ground root) was extracted twice using 50 mL of a mixture of methanol and water as follows: (1) 100% water, (2) 70:30 water:methanol, (3) 50:50 water:methanol, (4) 30:70 water:methanol, (5) 100% methanol. The extracts were combined, concentrated and dried under low vacuum. Identification of the chemical components was performed by HPLC using a Photo-Diode Array detector (HPLC-PDA), and a 250 mmx4.6 mm C18 column. The chemical components in each extract were quantified based on retention time and PDA data using baicalein, baicalin, scutellarein, and wogonin standards. The results are set forth in Table 10.

TABLE 10

| Quantification of Free-B-ring Flavonoids Extracted from<br><i>Scutellaria baicalensis</i> |                         |                                     |                                     |                            |
|-------------------------------------------------------------------------------------------|-------------------------|-------------------------------------|-------------------------------------|----------------------------|
| Extraction<br>Solvent                                                                     | Weight<br>of<br>Extract | %<br>Extractable<br>from<br>BioMass | Total<br>amount<br>of<br>Flavonoids | % Flavonoids<br>in Extract |
| 100% water                                                                                | 277.5 mg                | 27.8%                               | 1 mg                                | 0.09%                      |
| Water:methanol<br>(70:30)                                                                 | 538.5 mg                | 33.9%                               | 1.19 mg                             | 11.48%                     |
| Water:methanol<br>(50:50)                                                                 | 304.3 mg                | 33.4%                               | 1.44 mg                             | 18.93%                     |
| Water:methanol<br>(30:70)                                                                 | 294.9 mg                | 28.4%                               | 1.19 mg                             | 19.61%                     |
| 100% methanol                                                                             | 114.2 mg                | 11.4%                               | 2.73 mg                             | 24.81%                     |

## Example 14

[0209] Preparation of a Formulation with a Standardized Free-B-ring Flavonoid Extract from the Roots of *Scutellaria baicalensis* and a Standardized Flavonoid Extract from the Bark of *Acacia catechu*

[0210] A novel composition of matter, referred to herein as Univestin™, was formulated using two standardized extracts isolated from *Acacia* and *Scutellaria*, respectively, together with one or more excipients. A general example for preparing such a composition is set forth below. The *Acacia* extract used in this example contained >60% total flavans, as

catechin and epicatechin, and the *Scutellaria* extract contained >70% Free-B-ring flavonoids, which was primarily baicalein. The *Scutellaria* extract contained other minor amounts of Free-B-ring flavonoids as set forth in Table 11. One or more excipients is added to the composition of matter. The ratio of flavan and Free-B-ring flavonoids can be adjusted based on the indications and the specific requirements with respect to inhibition of COX-2 vs. 5-LO and potency requirements of the product. The quantity of the excipients can be adjusted based on the actual active content of each ingredient. A blending table for each individual batch of product must be generated based on the product specification and QC results for individual batch of ingredients. Additional amounts of active ingredients in the range of 2-5% are recommended to meet the product specification. Table 11 illustrates a blending table that was generated for one batch of Univestin™ (Lot #G1702-COX-2).

[0211] *Scutellaria baicalensis* root extract (38.5 kg) (lot #RM052302-01) having a Free-B-ring flavonoid content of 82.2% (baicalein); *Acacia catechu* bark extract (6.9 kg) (lot #RM052902-01) with total flavan content of 80.4%; and excipient (5.0 kg of Candex) were combined to provide a Univestin™ formulation (50.4 kg) having a blending ratio of 85:15. Table 9 provides the quantification of the active Free-B-ring flavonoids and flavans of this specific batch of Univestin™ (Lot #G1702-COX-2), determined using the methods provided in Examples 7 and 9.

TABLE 11

| Free-B-ring Flavonoid and Flavan Content of<br>Univestin™ Formulation |           |
|-----------------------------------------------------------------------|-----------|
| Active Components                                                     | % Content |
| Flavonoids                                                            |           |
| a. Baicalein                                                          | 62.5%     |
| b. Minor Flavonoids                                                   |           |
| i. Wogonin-7-glucuronide                                              | 6.7%      |
| ii. Oxxylin A-7-glucuronide                                           | 2.0%      |
| iii. Baicalein                                                        | 1.5%      |
| iv. Wogonin                                                           | 1.1%      |
| v. Chrysin-7-glucuronide                                              | 0.8%      |
| vi. 8-Methyl-wogonin-7-glucuronide                                    | 0.5%      |
| vii. Scutellarin                                                      | 0.3%      |
| viii. Norwogonin                                                      | 0.3%      |
| ix. Chrysin                                                           | <0.2%     |
| x. Oxxylin A                                                          | <0.2%     |
| c. Total Free-B-ring Flavonoids                                       | 75.1%     |
| d. Flavans                                                            |           |
| a. Catechin                                                           | 9.9%      |
| b. Epicatechin                                                        | 0.4%      |
| c. Subtotal Flavans                                                   | 10.3%     |
| d. Total Active Ingredients                                           | 85%       |

[0212] With reference to Table 9, this specific batch of Univestin™ contains 86% total active ingredients, including 75.7% Free-B-ring flavonoids and 10.3% flavans. Two different dosage levels of final product in capsule form were produced from this batch of Univestin™ (50.0 kg): 125 mg per dose (60 capsules) and 250 mg per dose (60 capsules). The final product was evaluated in a human clinical trial as described in Example 15.

[0213] Using the same approach, two other batches of Univestin™ were prepared using a combination of a stan-

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TABLE 14-continued

|                 | Change in Mean Weight (kg) and BMI (kg m <sup>-2</sup> ) at 30 and 90 Days |           |                   |           |                  |           |         |           |
|-----------------|----------------------------------------------------------------------------|-----------|-------------------|-----------|------------------|-----------|---------|-----------|
|                 | Group                                                                      |           |                   |           |                  |           |         |           |
|                 | Univestin™<br>250                                                          |           | Univestin™<br>500 |           | Celecoxib<br>200 |           | Placebo |           |
|                 | Mean                                                                       | Std. Dev. | Mean              | Std. Dev. | Mean             | Std. Dev. | Mean    | Std. Dev. |
| BMI-<br>30 days | -1.28                                                                      | 1.33      | -1.31             | 1.13      | -0.68            | 1.11      | -0.21   | .64       |
| BMI-<br>90 days | -1.84                                                                      | 1.14      | -1.39             | 1.04      | -1.17            | 1.07      | -0.12   | .54       |

[0237] Based on these data, the 250 mg/day dose of Univestin™ gave the greatest amount of weight loss and change in BMI followed by the 500 mg/day dose of Univestin™ and then celecoxib. The placebo had no effect on weight or BMI.

[0238] It is not believed that there are any other reports in the literature of anti-inflammatory compounds being used to effect weight loss or changes in BMI. Though the subjects were given no advice on exercise, the greater functional capabilities gained after treatment, especially with Univestin™, may have allowed them to exercise more on their own accord. Alternatively, Univestin™ may be increasing thermogenesis, lipolysis, or causing an under utilization of carbohydrates or fat in the diet. FIGS. 32 and 33 illustrate the BMI and weight loss seen for Univestin™ after 30 and 90 days of treatment.

#### Example 22

[0239] Clinical Evaluation of the Efficacy of Free-B-ring Flavonoids and Flavans on Lowering of Blood Glucose Due to an Increase in Function.

[0240] Blood glucose was also taken at 0 (baseline), 30 days and 90 days after treatment (see Example 20). These measurements were reported in mmole per liter. The data is also shown in mg/dl. Table 15 sets forth blood glucose levels after 30 and 90 days of treatment with Univestin™ at 250 and 500 mg/day.

TABLE 15

|                                    | Change in Blood Glucose after 30 and 90 days of Treatment |       |           |  |                |       |           |  |
|------------------------------------|-----------------------------------------------------------|-------|-----------|--|----------------|-------|-----------|--|
|                                    | Group                                                     |       |           |  |                |       |           |  |
|                                    | Univestin™ 250                                            |       |           |  | Univestin™ 500 |       |           |  |
|                                    | mmol/L                                                    | mg/dl | Std. Dev. |  | mmol/L         | mg/dl | Std. Dev. |  |
| Glucose-<br>Baseline               | 5.21                                                      | 94.32 | .71       |  | 5.24           | 94.32 | .87       |  |
| Glucose-<br>30 days                | 5.11                                                      | 91.81 | .71       |  | 4.75           | 85.51 | .65       |  |
| Glucose-<br>90 days                | 4.86                                                      | 87.64 | .71       |  | 4.34           | 78.12 | .36       |  |
| Percent<br>Change<br>By 90<br>days | -7.52                                                     |       |           |  | -12.79         |       |           |  |
|                                    |                                                           |       |           |  | .94            |       |           |  |

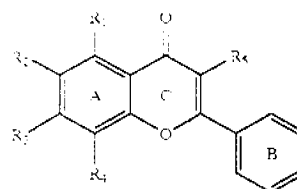
[0241] These data suggest that both the 250 and the 500 mg/day doses of Univestin™ are significantly lowering blood glucose levels over time. This impact may or may not be related to the loss of weight observed above or to the presumed increase in activity as functional impairment improved. It may also be possible that Univestin™ is acting directly to improve glucose metabolism by decreasing glucose tolerance or by utilizing carbohydrates more effectively.

1. A composition of matter comprised of a comprised of a mixture of at least one Free-B-ring flavonoid and at least one flavan.

2. The composition of claim 1 wherein the ratio of Free-B-ring flavonoid to flavan in said composition is selected from the range of 99:1 Free-B-ring flavonoid:flavan to 1:99 of Free-B-ring flavonoid:flavan.

3. The composition of claim 2 wherein the ratio of Free-B-ring flavonoid:flavan in the composition of matter is about 85:15.

4. The composition of claim 1 wherein said Free-B-ring flavonoid is selected from the group of compounds having the following structure:



wherein

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, and R<sub>5</sub> are independently selected from the group consisting of —H, —OH, —SH, —OR, —SR, —NH<sub>2</sub>, —NHR, —NR<sub>2</sub>, —NR<sub>3</sub><sup>+</sup>X<sup>-</sup>, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof,

wherein

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(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
20 June 2002 (20.06.2002)

PCT

(10) International Publication Number  
**WO 02/47615 A2**

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- (21) International Application Number: PCT/US01/49052
- (22) International Filing Date: 13 December 2001 (13.12.2001)
- (25) Filing Language: English
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- without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 02/47615 A2

(54) Title: ORAL COMPOSITIONS AND USE THEREOF

(57) **Abstract:** The present invention relates to an oral composition which includes an organoleptically suitable carrier and an amount of a terpenoid and a flavonoid, dispersed in the carrier, which is effective to prevent or treat dental caries, dental plaque formation, gingivitis, candidiasis, dental stomatitis, aphthous ulceration, or fungal infection. The invention also relates to various uses of oral compositions, containing a terpenoid, a flavonoid, or both, such uses include: inhibiting the activity of surface-bound glucosyltransferase, treating or inhibiting dental caries, gingivitis, candidiasis, denture stomatitis, inhibiting the accumulation of microorganisms on an oral surface, and/or treating or inhibiting aphthous ulcerations on an oral surface.

be of the type described above, present in the amount described above. The molar ratio of terpenoid:flavonoid can be between about 0.1 to about 10:1, preferably about 0.5 to about 5:1.

In addition, the oral composition can include a number of additives,  
5 including without limitation, an abrasive agent, a gelling agent, a humectant, a cariostatic agent, a flavoring agent or sweetener, a desensitizing agent, an anti-calculus agent, a whitening agent, a surfactant, a binding agent, a preservative, an opacifying agent, a coloring agent, a buffering agent, or combinations thereof.

Abrasive agents are typically employed in dentifrice compositions.  
10 Suitable abrasive agents include, without limitation, aluminum oxide, aluminum hydroxide, calcium hydrogen phosphate dihydrate or anhydride, silica gel, zirconosilicate, silicic anhydride, aluminosilicate, calcium carbonate, calcium pyrophosphate, aluminum silicate, insoluble sodium metaphosphate, magnesium tertiary phosphate, magnesium carbonate, calcium sulfate, synthetic resins, and  
15 combinations thereof. Abrasives can generally be employed in effective amounts of between about 20 to about 90 weight percent, more typically about 20 to about 60 weight percent for dentifrices.

Gelling agents (i.e., thickeners) can be used in various compositions to assist in processing. Suitable gelling agents include, without limitation, carrageenan,  
20 sodium carboxymethyl cellulose, alkali metal alginates such as sodium alginate, gums, polyvinyl alcohol, and vee gum or the like. Typically, the gelling agents are employed in amount of about 0.3 to about 5 weight percent.

Humectants can also be employed in the oral compositions, particularly toothpastes and gels and oral rinses. Suitable humectants include sorbitol,  
25 glycerin, propylene glycol, 1,3-butylene glycol, polyethylene glycol, xylitol, maltitol, lactitol, or the like. The humectant can also be used as the bulk carrier in many instances, in which case it can be present in an amount of about 5 to about 90 weight percent, more typically about 10 to about 60 weight percent.

Cariostatic agents (i.e., non-flavonoid cariostatic agents) can be  
30 provided in each form of the oral composition. Suitable cariostatic agents include, without limitation, **sodium fluoride**, stannous fluoride, aminefluorides, sodium

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monofluorophosphate, sodium trimeta-phosphate, triclosan, casein, or combinations thereof. If desired, the cariostatic agent can be present in an amount between about 0.01 to about 3 weight percent, more typically between about 0.02 to about 1 weight percent.

5                   Flavoring agents are desired in most oral compositions to enhance the flavor and palatability of the oral composition and, thus, the likelihood of their use. Suitable flavoring agents can be flavoring oils (e.g., oil of spearmint, peppermint, wintergreen, sassafras, clove, sage, eucalyptus, cinnamon, lemon, and orange, methyl salicylate, etc.) or sweeteners (e.g., sucrose, sucralose, lactose, maltose, xylitol, 10 sodium cyclamate, perillartine, aspartyl phenyl alanine methyl ester, saccharine, etc.). Flavoring agents can be present, either individually or collectively, in an amount of about 0.1 to about 10 weight percent, more typically about 0.1 to about 5 weight percent.

                  Desensitizing agents can be introduced in some embodiments of the 15 oral composition to treat individuals whose teeth are sensitive to thermal shock, chemicals, etc. Suitable desensitizing agents include, without limitation, potassium citrate, potassium chloride, potassium tartrate, potassium bicarbonate, potassium oxalate, potassium nitrate, and strontium salts. Desensitizing agents can be present, either individually or collectively, in an amount of about 0.1 to about 5 weight 20 percent, more typically about 0.1 to about 3 weight percent.

                  Anti-calculus agents can be introduced in some embodiments of the oral composition to treat tartar formation. Suitable anti-calculus agents include, without limitation, alkali-metal pyrophosphates, hypophosphite-containing polymers, organic phosphonates, phosphocitrates, and combinations thereof. Anti-calculus 25 agents can be present, either individually or collectively, in an amount of about 0.1 to about 5 weight percent, more typically about 0.1 to about 3 weight percent.

                  Whitening agents can be employed in some forms of the oral composition. Suitable whitening agent including urea peroxide, calcium peroxide, and hydrogen peroxide. Whitening agents can be employed in amounts of about 0.5 30 to about 5 weight percent.

antibacterial activity at concentrations used in this assay, with exception to baicalein (MIC values of 500  $\mu$ M).

Table 4: MIC and MBC values for Antibacterial Compounds Against Mutans Streptococci Strains<sup>a</sup>

| Test compounds        | <i>Streptococcus mutans</i> UA 159 |                  | <i>Streptococcus mutans</i> GS-5 |      | <i>Streptococcus sobrinus</i> 6715 |      |
|-----------------------|------------------------------------|------------------|----------------------------------|------|------------------------------------|------|
|                       | MIC <sup>a</sup>                   | MBC <sup>a</sup> | MIC                              | MBC  | MIC                                | MBC  |
| Terpenoid             |                                    |                  |                                  |      |                                    |      |
| <i>tt</i> -Farnesol   | 125                                | 500              | 125                              | 500  | 62.5                               | 250  |
| Flavone               |                                    |                  |                                  |      |                                    |      |
| Baicalein             | 500                                | >500             | 500                              | >500 | 500                                | >500 |
| Flavanones            |                                    |                  |                                  |      |                                    |      |
| Pinocembrin           | 250                                | >500             | 250                              | >500 | 250                                | 500  |
| Sakuranetin           | >500                               | >500             | >500                             | >500 | 500                                | >500 |
| Isosakuranetin        | 500                                | >500             | 500                              | >500 | 250                                |      |
| Dihydroflavonol       |                                    |                  |                                  |      |                                    |      |
| Pinobanksin-3-acetate | 500                                | >500             | 500                              | >500 | 250                                | >500 |

<sup>a</sup> Values in  $\mu$ M.

Chlorhexidine (positive control) showed MIC values between 1.1-2.2  $\mu$ M (1-2  $\mu$ g/ml) and MBC value of 8.9  $\mu$ M (8  $\mu$ g/ml).

Kaempferide, kaempferol, galangin, isorhamnetin, rhamnetin, fisetin, rutin, apigenin, acacetin, chrysin, luteolin, tectochrysin, ferulic acid, p-coumaric acid, caffeic acid,  $\beta$ -caryophyllene, terpineol, syringaldehyde, protocatechuic acid, vanillin, benzoic acid, pinobanksin, pinobanksin-7-methyl ether had MICs greater than 500  $\mu$ M.

5

For the compound with highest antibacterial activity, the time kill studies were performed by broth macrodilution method (National Committee for Clinical Laboratory Standards, Tentative standard M26-T, 1992). The starting inoculum of *S. mutans* GS-5 and UA 159, and *S. sobrinus* 6715 was  $1-5 \times 10^6$  CFU/ml. The final concentration of the antibacterial agent was 4 times MIC (or MBC values). Tubes containing the microorganisms and the test compound in TSB were incubated in 5% CO<sub>2</sub> at 37°C; samples were removed for viable counts at 0, 30 min., 1, 2, 4, 8, and 24 h. Serial dilutions ( $10^{-1}$  to  $10^{-4}$ ) were prepared in sterile 0.9% sodium chloride solution. The diluted sample (50  $\mu$ l) was plated on to tryptic soy agar by means of a spiral plater (Autoplate model 3000, Spiral Biotech, Inc., Bethesda, Md.). The plates were incubated in 5% CO<sub>2</sub> at 37 °C for 48h, when the number of colonies

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190**What Is Claimed:**

1. An oral composition comprising:  
an organoleptically suitable carrier; and  
5 an amount of a terpenoid and a flavonoid dispersed in the carrier, which is effective to prevent or treat dental caries, dental plaque formation, gingivitis, candidiasis, dental stomatitis, aphthous ulceration, or fungal infections.
2. The oral composition according to claim 1, wherein the carrier  
10 is selected from the group consisting of water, glycerin, alcohol, DMSO, a curable polymer, starch, and a combination thereof.
3. The oral composition according to claim 1, wherein the  
terpenoid is *n*-farnesol or its stereoisomers or derivatives,  $\beta$ -caryophyllene, terpineol,  
15 nerolidol, bisabolol, santalol, dehydroabietic acid, abietic acid,  $\beta$ -amyrine, triterpenic alcohol of amyrine, lanosterol, cupressic acid or its derivatives, agathic acid or its derivatives, agathalic acid, betulol, melliferone, moronic acid, anwuweizonic acid, betulonic acid, syringaldehyde, imbricatoloic acid, communic acid, methyl  
isocupressate, tremetone, viscidone or its derivatives,  $\delta$ -cadinene, ledol, guajol,  $\alpha$ -  
20 copaene,  $\beta$ -selinene,  $\alpha$ -elemene, calamenene,  $\alpha$ -muurolene,  $\gamma$ -muurolene,  $\beta$ -eudesmol, humulene, bulnesol, or a combination thereof.
4. The oral composition according to claim 1, wherein the  
flavonoid is apigenin or its derivatives, acacetin, baicalein, chrysin, luteolin,  
25 tectochrysin, kaempferol, kaempferide, galangin, isorhamnetin, rhamnetin, myricetin, fisetin, rutin, pinobanksin, pinobanksin-3-acetate, pinobanksin-7-methyl ether, pinocembrin, sakuranetin, isosakuranetin, quercetin, hesperitin, naringin, pinostrobin or its derivatives, trihydroxymethoxy flavanone, tetrahydroxy flavanone, tetrahydroxy flavone, ermanin, 3,5,7-trihydroxy-4'-methoxyflavanol, 5,6,7-trihydroxy-  
30 3,4'-dimethoxyflavone, 3,7-dihydroxy-5-methoxyflavanone, 2,5-dihydroxy-7-methoxyflavanone, 3-methylquercetin, 8-methylkaempferol, or a combination thereof.

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5. The oral composition according to claim 1, wherein the terpenoid is present in an effective amount of less than about 5 percent by weight/volume.

5

6. The oral composition according to claim 1, wherein the flavonoid is present in an effective amount of less than about 5 percent by weight/volume.

10

7. The oral composition according to claim 1, wherein the terpenoid:flavonoid molar ratio is between about 0.1 to about 10:1.

8. The oral composition according to claim 1 further comprising a cariostatic agent.

15

9. The oral composition according to claim 1 further comprising an abrasive agent, a gelling agent, a humectant, a cariostatic agent, a flavoring agent or sweetener, a desensitizing agent, an anti-calculus agent, a whitening agent, a surfactant, a binding agent, a preservative, an opacifying agent, a coloring agent, a buffering agent, or combinations thereof.

20

10. The oral composition according to claim 1, wherein the oral composition is a toothpaste or gel, a powder, a solution, a suspension, an emulsion, a lozenge, a mucoadhesive vehicle, a tablet, or a gum.

25

11. A method of inhibiting the activity of surface-bound glucosyltransferase comprising:

contacting a surface-bound glucosyltransferase with an effective amount of a flavonoid or a combination of a flavonoid and a terpenoid, under conditions effective to inhibit the glucan-forming activity of the surface-bound glucosyltransferase.

30

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**  
**DIRECCIÓN DE NUEVAS CREACIONES**

2020  
Bogotá, D.C.,

✓ Abogado: **JUAN PABLO CADENA SARMIENTO**

|        |            |          |
|--------|------------|----------|
| ASUNTO | Radicación | 07-63480 |
|        | Trámite    | 002      |
|        | Evento     | 378      |
|        | Actuación  | 519      |
|        | Oficio     |          |
|        | Folios     | 014      |

004010

Patente de Invención ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☐

Cap. I ☒

Cap. II ☐

No. Solicitud Internacional: PCT/US2005/046522

Fecha de Presentación Internacional: 2005-12-21

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 comunica:

**1. Documentos estudiados**

Descripción: Folios 56 a 86 como se radicó inicialmente.

Reivindicaciones: Folios 87 a 92 como se radicó inicialmente.

Prioridad: Folio 1 - US2004 60639331 (2004-12-22)  
US2005 11301098 (2005-12-12)

**2. Objeto de la invención**

Título de la solicitud: "Composiciones para el cuidado oral que contienen flavonoides y flavanos".

El problema planteado en esta solicitud es la necesidad de composiciones de cuidado oral útiles para la prevención y tratamiento de inflamaciones

Para resolver este problema técnico la solicitud en estudio proporciona una composición que contiene como compuestos activos flavonoides de anillo B y flavanos.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A61K8/19; A61K8/21; A61P29/00; A61Q11/00; A61Q11/02

**3. Excepción a la Patentabilidad (Art 20 D 486 literal (d))**

El objeto de las reivindicaciones 44- 47 no es patentable de acuerdo con el Art citado.

4. De la Solicitud de Patente

4.1.Reivindicaciones (Art 30 D 486, Art 22 PCT)

Claridad

Las reivindicaciones 2, 5, 14, 17, 20, 22, 23, 29, 31, 33 y 38 contienen los términos: “alrededor de, por lo menos de”; dichos términos son imprecisos por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.

Concisión

Las reivindicaciones 1-3, 12-15, 28, 29, 38, 39 y 43 contienen los términos “agente realizador de la biodisponibilidad”, “agente realizador de la eficacia”, “agente realizador de la retención”, “agente realizador de estabilidad”; los cuales son términos imprecisos y no permiten conocer a que tipo de sustancia química se refiere. De igual manera, no permiten hacer una comparación con el estado de la técnica. Se sugiere modificar dichas reivindicaciones definiendo químicamente cada uno de los agentes preferidos.

Las Reivindicaciones 4, 10, 16, 19, 20, 24, 27, 30, 34, 37, 41 no son concisas porque hacen referencia a una selección de compuestos de diferente tipo y naturaleza para diferentes actividades, lo anterior no define la composición reivindicada, ni limita el alcance de la invención. Así mismo no permite hacer una comparación con el estado de la técnica.

Se requiere al Solicitante hacer las aclaraciones necesarias.

5. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la Fecha de Presentación de la Solicitud de Prioridad (Diciembre 22 de 2004) y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento      | Título                                                                                | Fecha de Publicación |
|------|----------------|---------------------------------------------------------------------------------------|----------------------|
| D1   | US2003/0216481 | Formulation of a mixture of free-B-ring flavonoids and flavans as a therapeutic agent | Noviembre 20 de 2003 |
| D2   | WO0247615      | Oral composition and use thereof                                                      | Junio 20 de 2002     |

D1 divulga una composición oral para el tratamiento de inflamaciones que comprende un flavonoide de anillo B libre y un flavano con excipientes adecuados.

D2 divulga una composición oral para el tratamiento de gingivitis, placa y caries dental que comprende un flavonoide de anillo B libre y un terpenoide en un vehículo organolépticamente aceptable.

6. Análisis de Patentabilidad (Art 14 D486)

6.1.Novedad (Art 16 D486)

La reivindicación 1 consiste en una composición oral que comprende

- Un flavonoide de anillo –B libre;
- Un flavano; y
- Un agente realizador de la biodisponibilidad para el flavonoide y/o flavano

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

| Características esenciales      | D1 | D2 |
|---------------------------------|----|----|
| <b>Composición oral</b>         | √  | √  |
| - Flavonoide de anillo B libre  | √  | √  |
| - Flavano                       | √  | √  |
| - Agente realzador (excipiente) | √  | √  |

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual enseña una **composición oral** (folio 133) que comprende un:

- Un flavonoide de anillo –B libre (folio 135, párrafos 0210- 0211, tabla 9, reivindicación 1);
- Un flavano (folio 135, párrafos 0210- 0211, tabla 8, reivindicación 1); y
- Un agente realzador de la biodisponibilidad para el flavonoide y/o flavano como es un dextrano (Candex) (folio 133, párrafos 0157-0158; folio 135 párrafo 0211).

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

La **reivindicación 12** consiste en una composición oral que comprende

- Un flavonoide de anillo –B libre;
- Un flavano;
- Un agente realzador de la biodisponibilidad para el flavonoide y/o flavano; y
- Un agente antibacteriano no iónico

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

| Características esenciales        | D1 | D2 |
|-----------------------------------|----|----|
| <b>Composición oral</b>           | √  | √  |
| - Flavonoide de anillo B libre    | √  | √  |
| - Flavano                         | √  | √  |
| - Agente realzador (excipiente)   | √  | √  |
| - agente antibacteriano no iónico | -  | √  |

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en **D2** que divulga una composición oral (folios 137, 141) comprende:

- un flavonoide de anillo B libre (reivindicaciones 1, 4 y 6);
- un flavano (reivindicaciones 1, 3) y
- un agente activo antibacterial no ionico y anti placa (reivindicaciones 8 y 9) dentro de los que se encuentra el triclosan (folio 139, línea 1) dentro de un vehiculo farmacéuticamente aceptable que contiene un agente realzador de la biodisponibilidad (reivindicación 2).

En consecuencia, la reivindicación 12 carece de novedad, según lo divulgado en el documento D2.

La **reivindicación 21** consiste en una composición oral que comprende

- Un flavonoide de anillo –B libre;
- Un flavano; y
- Un agente activo para el cuidado oral

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

| Características esenciales       | D1 | D2 |
|----------------------------------|----|----|
| <b>Composición oral</b>          | √  | √  |
| - Flavonoide de anillo B libre   | √  | √  |
| - Flavano                        | √  | √  |
| - agente activo (antibacteriano) | -  | √  |

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en **D2** que divulga una composición oral (folios 137, 141) comprende:

- un **flavonoide de anillo B libre** (reivindicaciones 1, 4 y 6);
- un **flavano** (reivindicaciones 1, 3) y
- un **agente activo** dentro de los que se encuentran antibacteriales, anti placa, balnqueadores, etc (reivindicaciones 8 y 9).

En consecuencia, la reivindicación 21 carece de novedad, según lo divulgado en el documento D2.

La **reivindicación 32** consiste en una composición oral que comprende

- Un flavonoide de anillo –B libre;
- Un flavano; y
- Un agente activo para el cuidado oral que comprende una fuente de ion estañoso.

Comparación de las características técnicas **esenciales**, con las del estado de la Técnica:

| Características esenciales            | D1 | D2 |
|---------------------------------------|----|----|
| <b>Composición oral</b>               | √  | √  |
| - Flavonoide de anillo B libre        | √  | √  |
| - Flavano                             | √  | √  |
| - agente activo (fuente ion estañoso) | -  | √  |

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en **D2** que divulga una composición oral (folios 137, 141) comprende:

- un **flavonoide de anillo B libre** (reivindicaciones 1, 4 y 6);
- un **flavano** (reivindicaciones 1, 3) y
- un **agente activo** dentro de los que se encuentran anti caries, antibacteriales, anti placa, balnqueadores, etc (reivindicaciones 8 y 9) como lo son las **fuentes de ion estañoso** ( floruro de estaño ) (folio 138, línea 31).

En consecuencia, la reivindicación 21 carece de novedad, según lo divulgado en el documento D2.

A partir de lo anterior las reivindicaciones independientes 1, 12, 21 y 32 con sus reivindicaciones dependientes carecen de novedad.

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7. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

| Item | Documento      | Reivindicaciones afectadas | Requisito que afecta |
|------|----------------|----------------------------|----------------------|
| D1   | US2003/0216481 | 1                          | Novedad              |
| D2   | WO0247615      | 1, 12, 21, 32, 39          | Novedad              |

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 60 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 N° 10 de 2001.

  
**JOSÉ LUIS SALAZAR LÓPEZ**  
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha  
04 MAR 2011

|                                    |                                               |
|------------------------------------|-----------------------------------------------|
| <b>CONCEPTO TÉCNICO</b><br>No.0036 | <b>EXAMINADOR TÉCNICO</b><br>Código No.202093 |
|------------------------------------|-----------------------------------------------|