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## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 7/50, 7/06, 7/48</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 96/29983</b> <b>(43) International Publication Date:</b> 3 October 1996 (03.10.96)
<b>(21) International Application Number:</b> PCT/US96/03821 <b>(22) International Filing Date:</b> 21 March 1996 (21.03.96) <b>(30) Priority Data:</b> 08/411,883 31 March 1995 (31.03.95) US <b>(71) Applicant (for all designated States except US):</b> COLGATE-PALMOLIVE COMPANY [US/US]; 300 Park Avenue, New York, NY 10022 (US). <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> RAMACHANDRAN, Pallassana, N. [US/US]; 28 Dunbar Drive, Robbinsville, NJ 08691 (US). ROBBINS, Clarence, R. [US/US]; 1726 Woodfield Road, Martinsville, NJ 08836 (US). PATEL, Amrit, M. [US/US]; 35 Wetherhill Way, Dayton, NJ 08810 (US). <b>(74) Agent:</b> ANCEL, Richard, J.; Colgate-Palmolive Company, 909 River Road, Piscataway, NJ 08855-1343 (US).		<b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), 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).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> SKIN CARE PRODUCTS CONTAINING ANTI-ITCHING/ANTI-IRRITANT AGENTS		
<b>(57) Abstract</b>		
<p>Mild aqueous detergent, e.g., shampoo, compositions are disclosed based on a mixture comprising anionic surfactant and amphoteric surfactant, such as betaines, present in the composition at a level of from about 0.75 to 1.25 parts by weight per part by weight of anionic surfactant. The compositions also contain one or a mixture of climbazole and one or more co-therapeutics such as salicylic acid. The combination of mild surfactant system and therapeutic agent serve to prevent or treat mild skin disorders such as scalp itch and scalp irritation when applied to the scalp as a shampoo. Shampoo compositions also preferably contain one or more conditioning agents and suitable suspending agents. The invention also provides a method for treating dry skin comprising applying certain of the therapeutic agents to dry skin to promote the natural secretion of sebum.</p>		

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SKIN CARE PRODUCTS CONTAINING  
ANTIITCHING/ANTIIRRITANT AGENTS

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BACKGROUND OF THE INVENTION

Field of the Invention

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The invention relates to skin care compositions which exhibit a therapeutic effect in the treatment of skin disorders such as itching, irritation and skin dryness.

Description of Related Art

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There are a number of shampoo products on the market today which are specifically formulated as anti-dandruff shampoos. These products generally contain one or a mixture of surfactants, with the primary surfactant being an anionic surfactant such as an alkyl or aryl sulfate or sulfonate. One hypothesis is that dandruff problems are believed to be linked to the presence of a yeast-like fungus on the skin and an acceleration of the normal process of skin production. Conventional anti-dandruff shampoos generally contain effective amounts of an active agent which inhibits fungal growth and/or slows cell growth on the scalp. Examples of these agents include zinc pyrithione, selenium sulfide, salicylic acid, coal tar, sulfur, ketoconazole and climbazole. Examples of typical anti-dandruff shampoo formulations are disclosed in U.S. Patents 4,089,945; 4,329,334; 4,329,335; 4,329,336 and 4,835,148.

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However, experience has shown that excessive dandruff is largely a problem associated with cold, dry climates and it generally does not occur until after puberty. In more humid, tropical regions dandruff is a much less common disorder. However, inhabitants of these regions are generally more susceptible to mild forms of scalp dermatitis with such symptoms as excessive scalp itching,

scalp irritation, inflammation, scalp dryness and scalp redness. These symptoms can also occur during the warm summer months in non-tropical regions. Although many of these symptoms ought to be relieved by the use of the anti-fungal agents present in some anti-dandruff shampoos, e.g., climbazole, zinc pyrithione or selenium sulfide, experience has demonstrated that these symptoms are not relieved and, in fact, are even worsened by regular use of many commercial anti-dandruff hair shampoos.

Accordingly it is a primary object of this invention to provide a mild, aqueous, skin care detergent composition, e.g., a scalp care shampoo or a shower cleansing composition, which exhibits a therapeutic effect on skin disorders, particularly, scalp disorders, particularly as encountered in warm weather and in tropical regions.

It is another object of the invention to provide a skin care product for the treatment of dry skin, other than scalp skin, which promotes the natural secretion of sebum.

#### SUMMARY OF THE INVENTION

The present invention provides a mild aqueous, detergent composition, e.g., a shampoo composition, having a therapeutic effect on skin and scalp disorders comprising an aqueous dispersion of: (a) from about 5 to about 12% by weight of anionic surfactant; (b) amphoteric surfactant present in said composition at a level of at least about 0.75 parts by weight per part by weight of said anionic surfactant; and (c) from about 0.10 to about 4% by weight of a therapeutic agent selected from the group consisting of 1-imidazolyl-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one, (climbazole) acetylsalicylic acid, salicylic acid, 2,4,4,'-trichloro-2'-hydroxy diphenyl ether (triclosan); 1-acetyl-4-(4-((2-(2,4-dichlorophenyl)-2-(1H-imidazolyl-1-methyl)-1,3-dioxolan-

4-yl)methoxy)phenyl)-piperazine (Ketoconazole); 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone monoethanolamine salt (picrotone olamine); selenium sulfide; zinc pyrithione; coal tar; sulfur; 2-(4'-isobutylphenyl) propionic acid (ibuprofen); and mixtures thereof.

The invention also provides for a method of treating scalp disorders such as scalp irritation and/or itching comprising applying to the hair and scalp compositions of the invention as a shampoo and rinsing the shampoo from the hair after shampooing.

Therapeutic testing of individuals living in tropical climates has demonstrated that the detergent compositions of the invention, particularly in the form of shampoos, serve both to prevent the onset of minor scalp disorders in individuals previously free of disorder and to provide therapeutic healing of such disorders in individuals presented with such disorders.

#### DETAILED DESCRIPTION OF THE INVENTION

Anionic surfactants normally present in mild detergent compositions, especially shampoo formulations are used not only for deterative or cleansing performance, but because they impart a high degree of foaming characteristics to the detergent composition or shampoo, which enhances consumer appeal. However, the anionics are generally much more irritating to the skin than are the amphoteric or non-ionic surfactants. On the other hand, these latter surfactant types are considerably less foaming than the anionics and are thus less appealing when used as a major or sole surfactant component in a detergent composition or a shampoo.

The present invention is grounded on the discovery that use of a specific combination of anionic and amphoteric surfactants provides a mild surfactant base for a

therapeutic aqueous, body cleansing composition, particularly in the form of a shampoo, such that the surfactant system does not tend to counteract or negate the therapeutic benefits afforded by the therapeutic agents present in the body cleansing composition or shampoo.

Suitable anionic surfactants which may be used include the water-soluble alkali metal or ammonium salts having alkyl radicals containing from about 8 to about 22 carbon atoms, the term alkyl being sued to include the alkyl portion of higher acyl radicals. Examples of suitable synthetic anionic surfactants are sodium or ammonium alkyl sulphates, especially those obtained by sulphating higher (C<sub>8</sub>-C<sub>18</sub>) alcohols produced, for example, from tallow or coconut oil; alkyl (C<sub>9</sub>-C<sub>20</sub>) benzene sulfonates, particularly sodium linear secondary alkyl (C<sub>10</sub>-C<sub>15</sub>) benzene sulfonates; alkyl glycerol ether sulfates, especially those ethers of the higher alcohols derived from tallow or coconut oil and synthetic alcohols derived from petroleum; coconut oil fatty monoglyceride sulfates and sulfonates; salts of sulfuric acid esters of higher (C<sub>8</sub>-C<sub>18</sub>) fatty alcohol-alkylene oxide, particularly ethylene oxide reaction products; the reaction products of fatty acids such as coconut fatty acids esterified with isethionic acid and neutralized with sodium hydroxide; sodium and potassium salts of fatty acid amides of methyl taurine; alkane monosulfonates such as those derived from reacting alpha-olefins (C<sub>8</sub>-C<sub>20</sub>) with sodium bisulfite and those derived from reacting paraffins with SO<sub>2</sub> and Cl<sub>2</sub> and then hydrolyzing with a base to produce a random sulfonate; and olefin sulfonates which term is used to describe the material made by reacting olefins, particularly C<sub>10</sub>-C<sub>20</sub> alpha-olefins, with SO<sub>3</sub> and then neutralizing and hydrolyzing the reaction product. The preferred anionic surfactants are sodium or ammonium (C<sub>10</sub>-C<sub>18</sub>) alkyl sulfates and (C<sub>10</sub>-C<sub>18</sub>) alkyl polyethoxy (1-11 Eo) sulfates and mixtures thereof having differing water solubilities.

5 Particularly preferred anionic surfactant comprises a mixture of a C<sub>10</sub> to C<sub>18</sub> alkyl sodium or ammonium sulfate or sulfonate or a C<sub>14</sub>-C<sub>18</sub> alpha-olefin sodium or ammonium sulfonate (AOS) and a C<sub>8</sub> to C<sub>12</sub> alkyl polyethoxy (2-4 EO) sodium or ammonium sulfate. Mixtures containing a major amount of the alkyl sulfates, olefin sulfonates or alkyl alkoxy sulfates with aryl sulfonates such as sodium cumene sulfonate, sodium xylene sulfonate and sodium benzene sulfonate are also preferred.

10 The amount of anionic surfactant present in the composition will generally range from about 4 to 12% by weight (active ingredient), more preferably from about 6 to 10% by weight.

15 The second essential component of the formulation is an amphoteric surfactant, present at a level of at least about 0.75 parts by weight per 1 part by weight of the content of anionic surfactant present in the composition. The preferred level of amphoteric surfactant is in the range of from about 0.75 to 1.25 parts by weight, more preferably from about 0.9 to 1.1. parts by weight per 1 part by weight of anionic surfactant. It has been found that the presence of one or more amphoteric surfactants at these levels tends to cancel out the tendency of most anionic surfactants to cause irritation when contacted with the skin or scalp.

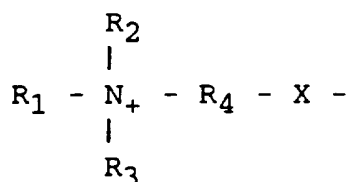
20 Examples of amphoteric surfactants which may be used in the compositions of the invention include betaines and compounds which can be broadly described as derivatives of aliphatic secondary and tertiary amines in which the aliphatic radical can be straight chain or branched and wherein one of the aliphatic substituents contains from about 8 to about 18 carbon atoms and one contains an anionic water solubilizing group, e.g., carboxy, sulfonate, sulfate, phosphate, or phosphonate. Examples of compounds falling within this definition are sodium 3-

dodecylaminopropionate, sodium 3-dodecylaminopropane sulfonate, N-alkyltaurines, such as prepared by reacting dodecylamine with sodium isothionate, N-higher alkyl aspartic acids and the products sold under the trade name "Miranol".

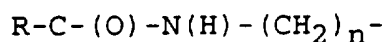
Examples of betaines useful herein include the high alkyl betaines such as coco dimethyl carboxymethyl betaine, lauryl dimethyl carboxymethyl betaine, lauryl dimethyl alpha-carboxymethyl betaine, cetyl dimethyl carboxymethyl betaine, lauryl bis(2-hydroxypropyl) carboxymethyl betaine, oleyl dimethyl gamma-carboxypropyl betaine, lauryl bis-(2-hydroxypropyl) alpha-carboxymethyl betaine and the like.

Other suitable sulfobetaines include 1-(lauryl, dimethylammonio) acetate-1-(myristyl dimethylammonio) propane-3-sulfonate and 1-(myristyl dimethylamino)-2-hydroxypropane-3-sulfonate.

Particularly preferred betaines are those having the following general formula:



wherein  $R_1$  is an alkyl group having from about 10 to 20 carbon atoms, preferably 12 to 16 carbon atoms or the amino radical:



wherein R is an alkyl group having about 10 to 20 carbon atoms and n is the integer 1 to 4;  $R_2$  and  $R_3$  are each alkyl groups having 1 to 3 carbons and preferably 1 carbon;  $R_4$  is an alkylene or hydroxyalkylene group having from 1 to 4 carbon atoms and, optionally, one hydroxyl group; and X is an anion selected from the group



consisting of  $\text{SO}_3^-$  and  $\text{COO}^-$ . Typical alkyl-dimethyl betaines include decyl dimethyl betaine or 2-(N-decyl-N,N-dimethylammonio) acetate, coco dimethyl betaine or 2-(N-coco-N,N-dimethyl-ammonio) acetate, myristyl dimethyl betaine, cetyl dimethyl betaine, stearyl dimethyl betaine, etc. Typical sulfobetaines or sultaines similarly include coco dimethyl sulfobetaine, or 3-(N-coco-N,N-dimethyl ammonio) propane-1 sulfonate, myristyl dimethyl sulfobetaine, or 3-(N-coco-N,N-dimethyl ammonio) propane-1 sulfonate, myristyl dimethyl sulfobetaine, palmityl dimethyl sulfobetaine, lauryl dimethyl sulfobetaine, etc. The amidobetaine and amidosulfobetaines similarly include cocoamidoethyl betaine, cocoamidoethylsulfobetaine, cocoamidopropyl betaine, cocomidopropylsulfobetaine and like materials.

Shampoo formulations containing a combination of anionic and amphoteric surfactants such as betaines present at a level of at least about 0.75 parts by weight betaine per part by weight of anionic surfactant are disclosed in copending U.S. Patent Appl. S.N. 08/155,251, the complete disclosure of which is incorporated herein by reference.

The composition may also contain one or more non-ionic surfactants which assist in the formation of more stable aqueous compositions, which compositions may be in the form of solutions or dispersions, particularly suspensions or emulsions. The non-ionics, where used, are generally present as a surfactant minor, generally at levels below 10% by weight, more preferably below 5% by weight of the composition.

Suitable nonionic surfactants include, in particular, the reaction products of compounds having a hydrophobic group and a reactive hydrogen atom, for example aliphatic alcohols, acids, amides and alkyl phenols with alkylene oxides, especially ethylene oxide, either alone or with propylene oxide. Specific nonionic surfactant compounds are alkyl ( $\text{C}_6$ - $\text{C}_{18}$ ) primary or secondary linear or

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branched alcohols condensed with ethylene oxide, and products made by condensation of ethylene oxide with the reaction products of propylene oxide and ethylenediamine. Other so-called nonionic surfactant compounds include long chain tertiary amine oxides, long-chain tertiary phosphine oxides, dialkyl sulfoxides, fatty (C<sub>8</sub>-C<sub>18</sub>) esters of glycerol, sorbitan and the like, alkyl polyglycosides, ethoxylated glycerol esters, ethoxylated sorbitans and ethoxylated phosphate esters.

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A more detailed illustration of the various surfactants and classes of surfactants mentioned may be found in the text Surface Active Agents, Vol. II, by Schwartz, Perry and Berch (Interscience Publishers, 1958), in a series of annual publications entitled McCutcheon's Detergents and Emulsifiers, issued in 1969, or in Tenside-Taschenbuch, H. Stache, 2nd Ed. Carl Hanser Verlag, Munich and Vienna, 1981.

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The therapeutic agent present in the composition is selected from the group consisting of climbazole, acetylsalicylic acid, salicylic acid, triclosan, ketoconazole, piroctone olamine, selenium sulfide, zinc pyrithione, coal tar, sulfur, ibuprofen and mixtures thereof, present at a level of from about 0.10 to about 4% by weight.

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The therapeutic agent preferably present in the composition of the invention is climbazole which is known chemically as 1-imidazolyl-1-(4-chlorophenoxy)-3,3-dimethylbutane-2-one or equivalent imidazolyl compounds. This agent may be prepared by reacting 1-bromo-1-(4-chlorophenoxy)-3-dimethylbutan-2-one with imidazole dissolved in acetonitrile as disclosed in U.S. Patent Nos. 3,812,142 and 3,903,287. This imidazolyl ketone is a water insoluble crystalline powder having a melting point of 94.5°-97.8°C, and may be obtained from the Bayer Company.

Climbazole has proven a more effective therapeutic in compositions having a pH on the acid side, e.g. from about 4.0 to about 6.9, more preferably from about 4.5 to 6.5. Adjustment of the pH of the shampoo formulation with a suitable acid, e.g. citric acid, may be necessary. Suitable acid buffers such as boric acid and phosphoric acid may also be used.

A combination of climbazole with one or more keratolytic or anti-inflammatory agents such as acetylsalicylic acid (aspirin), salicylic acid, 2,4,4'-trichloro-2'-hydroxy diphenyl ether (triclosan); 2-(4'-isobutylphenyl) propionic acid (ibuprofen); 1-acetyl-4-(4-((2-(2,4-dichlorophenyl)-2-(1H-imidazolyl-1-methyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-piperazine (Ketoconazole); 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone monoethanolamine salt (piroctone olamine); coal tar; selenium sulfide; sulfur or zinc pyrithione is also within the scope of the invention. Addition of one or more of these therapeutics serves the dual roles of pH adjustment (where the additive is acid) as described above, and as a co-therapeutic along with the climbazole. Use of the combination can also impart improved hair conditioning effects to the shampoo as will be hereinafter described. The climbazole is normally present in the shampoo at a level effective to provide therapeutic relief of the scalp disorders described herein. Preferred levels are in the range of about 0.1 to about 4% by weight, more preferably from about 0.25 to 2.5% by weight and most preferably from about 0.5 to 1.5% by weight. When used with a co-therapeutic, e.g. salicylic acid, the co-therapeutic may be present at a level of from about 0.1 to about 10% by weight, more preferably from about 0.25 to about 4% by weight and most preferably from about 0.25 to 2.5% by weight.

The body cleansing composition of the present invention may also be formulated as a hair conditioning shampoo and

therefore may contain one or more hair conditioning agents and suspending agents.

5        Suitable hair conditioning agents include organosilicon compounds, e.g., non-volatile silicones and aminosilicones such as dimethicone. The conditioner may also comprise water insoluble polyethylenes; paraffins; petrolatums; microcrystalline waxes; C<sub>18</sub>-C<sub>36</sub> mixed fatty acids and corresponding triglycerides; stearyl stearate  
10       and like known conditioners.

Conditioners may also include various cationic quaternary ammonium salts or polymers. Preferred quaternary ammonium salts include materials such as tricetyl methyl  
15       ammonium chloride, dicetyl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, tristearyl methyl ammonium chloride and other quaternaries such as: guar hydroxypropyl trimethylammonium chloride (Cosmedia GUAR-C261, available from Hoechst Celanese Corp.);  
20       polyethylene glycol (PEG 15) coco-polyamine (Polyquat® H81, available from Henkel G.m.b.H.); quaternized hydroxyethyl cellulose, available from Amerchol as Polymers JR and LR; polymers of dimethyldiallyl ammonium chloride or copolymers thereof with acrylamide, available  
25       as Merquats 100 and 550 (also known as polyquaternium 10 and 7 respectively); vinyl imidazole vinyl pyrrolidone copolymers, available as Luviquats from BASF Corp.; polyvinyl pyrrolidone-dimethylaminoethyl methacrylate copolymers, available as GAFQUATS from GAF Corp.; and  
30       like materials. The quaternary conditioners are normally present in the composition at levels of from about 0.2 to about 5% by weight.

35       Hair conditioning shampoos also contain one or more suspending agents or lipids which assist in maintaining a stable dispersion of non-water soluble ingredients and also impart improved hair conditioning effects, generally present at a level of from about 1 to 15% by weight. Suitable of such agents include long chain acyl

5 derivatives such as C<sub>16</sub> to C<sub>50</sub> fatty acid esters of polyols such as glycerol, ethylene glycol or sorbitol. Preferred agents of this class include glycerol distearate and isosteareth (2 or 10), as well as long chain alkanolamides such as stearamide DEA distearate. Suspending agents of this type are normally present in the composition at a level of from about 0.5 to about 5% by weight of the composition.

10 Other useful suspension stabilizers are long chain primary alcohols or ethoxylated alcohols averaging about 26 to 40 carbon atoms in the chain. These alcohols are mixed alcohols wherein at least about 80% of the chain lengths are of 18-44 carbon atoms for alcohols averaging  
15 30 carbon atoms and at least 80% of the chain lengths are 30-54 carbon atoms for alcohols averaging 40 carbon atoms. These materials are available from Petrolite Corporation under the trade name UNILIN<sup>TM</sup> alcohols. Preferred materials are Unilin<sup>TM</sup> 425 alcohol (30 carbon chain average), Unilin<sup>TM</sup> 550 alcohol (40 carbon chain average) and Unilin<sup>TM</sup> 350 (26 carbon chain average). A suitable derivative is Unithox<sup>TM</sup>-550 which is an  
20 ethoxylated (13 Eo) alcohol averaging 40 carbon atoms in the alkyl chain. These alcohols are normally present in the composition at levels of from about 1 to about 7% by weight.  
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30 The shampoo composition also contains water, preferably deionized or irradiated water. The amount of water present in the composition as added water plus water present in the ingredients used in the formula will generally range from about 50 to about 85% by weight, more preferably from about 60 to about 80% by weight.

35 In addition to the previously mentioned constituents of the liquid shampoo, normal and conventional adjuvants may be present, provided they do not adversely affect the properties of the shampoo. Thus, there may be used various coloring agents and perfumes, ultraviolet light

absorbers such as the Uvinuls, which are products of GAF Corporation, preservatives such as formaldehyde or hydrogen peroxide; pearlescing agents and opacifiers, solvents, such as ethanol, glycerin and glycols (ethylene glycol is useful as a clarifying agent, to prevent high and low temperature clouding of desirably clear shampoos); lubricants, such as mineral oil and higher fatty alcohols, e.g. cetyl alcohol, stearyl alcohol; sequestering agents such as EDTA tetrasodium salt, thickening agents such as hydroxypropyl methyl cellulose (Methocel 34M) and salts such as sodium chloride, etc. The proportion of such adjuvant material, in total, will normally not exceed 5% of the shampoo.

The shampoos are readily made by simple mixing methods from readily available components which, on storage, do not adversely affect the entire composition. However, it is preferred that the imidazolyl compound be first mixed with a nonionic component prior to the addition of the amphoteric and anionic surfactants. However, in the absence of a nonionic surfactant, the Climbazole can also be mixed with an aqueous solution of the amphoteric betaine prior to the addition of the anionic surfactant. Thus, the products are capable of being made in desired clear form or in opaque or opalescent form. The viscosities are adjustable by changing the total percentage of active ingredients and by modifying the percentages of thickening agent, sodium chloride and other adjuvants. The viscosity of the shampoo will normally be about that of glycerin at room temperature, e.g., about 1,000 centipoises, but the viscosity may be in the broader ranges of 250-1500 centipoises. Its viscosity may approximate those of commercially acceptable shampoos now on the market. Instead of measuring viscosity directly, as by a Brookfield LVF viscometer, one may employ standard laboratory flow tests, in which flow times through a restriction or tube length under a reproducible head are measured in seconds, utilizing a Raymond tube. Viscosities may preferably

range from 10-135 seconds and up to 300 or 400 seconds. The shampoo itself remains stable on storage for lengthy periods of time, without color changes or settling out of any insoluble materials.

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The following examples are illustrative of the invention.

Example 1

10 A shampoo composition was prepared by the general mixing procedure described above. The formulation of this shampoo is as follows in weight %:

	<u>COMPONENT</u>	<u>AS IS</u>	<u>%</u>
15	<u>ACTIVES</u>		
	Cocoamido Propyl Betaine No. 3	30.0	9.0
	Deionized water (irradiated)	25.0	--
	Sodium Deceth Sulfate (3 Eo)	15.0	4.5
	Ammonium Lauryl Sulfate	12.0	3.0
20	Sodium Cumene Sulfonate	5.0	2.3
	C <sub>30</sub> -C <sub>40</sub> Fatty Alcohol (UNILIN™)	4.0	4.0
	Dimethyl Polysiloxane	3.5	3.5
	Distearyl Methyl Ammonium Chloride	1.0	1.0
	Preservative	1.0	1.0
25	Isosteareth (2 Eo)	0.8	0.8
	Perfume	0.75	0.75
	Hydroxy Ethyl Cellulose	0.6	0.6
	Climbazole	0.5	0.5
	Polyquaternium 10	0.35	0.35
30	Sodium Phosphate (Di Basic)	0.2	0.2
	EDTA	0.1	0.06
	Colorant	0.013	0.013

This shampoo was designated as Formula A.

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Example 2

A second shampoo was prepared having the formula of Example 1 except that the amount of climbazole was raised

to 1.5% by weight and 1.5% by weight less water was added to the formulation. This formulation was designated as Formula B.

5 The effectiveness of the shampoo formulations of the present invention for healing and preventing scalp disorders was evaluated using the following protocol. Ninety residents of the Dominican Republic who were free of scalp disease (as determined by a dermatologist), but  
10 who regularly complained of scalp irritation and itching occasioned by shampoo usage were selected by questionnaire. The group was arbitrarily divided into six groups of 15 each.

15 Four groups were used to evaluate the effectiveness of Formulas A and B above in reducing scalp discomfort (itchiness) for those complaining of discomfort after shampooing with a control formulation containing a high content of anionic surfactant. The control formulation  
20 used was a formulation containing no therapeutic agent and a surfactant mixture high in anionic content. The surfactant combination (actives) in the control were:

25	Ammonium lauryl sulfate	- 19 wt.%
	Cocamide DEA*	- 4.5 wt.%
	Sodium cumene sulfonate	- 1.4 wt.%
	Na laureth -13 carboxylate	- 2.5 wt.%

\*CTFA adopted name for Coconut Diethanolamide

30 Each of the four panels were shampooed with the control product every other day for two weeks for a total of seven washes. The shampoo procedure involved the application of 10 grams of the control directly to the wet scalp followed by a one minute massage into the  
35 scalp. The hair is then washed and rinsed free of lather and dried.

Scalp evaluations were made by the subjects themselves and a dermatologist after 6, 10 and 14 days to determine



the degree of scalp discomfort occasioned by shampooing using the control. Ratings of itching, irritation (redness of skin), dryness and flaking were made on a scale of 1 to 10, with 1 representing no problem and 10 representing maximum problem.

The average score for each of the four groups at the end of the control washing for each of the four scalp discomfort factors was plotted as a base line value.

The four control groups were then subjected to seven additional shampoos using the protocol described above over the next two weeks using the following shampoos:

Group A - Formula A.

Group B - Formula B.

Group C - Commercial HEAD AND SHOULDERS™ product obtained in Mexico (H&S)\*

Group D - Commercial PANTENE™ Scalp Care/Anti Dandruff product obtained in the Philippines.\*

\* Major surfactant is anionic.

Scalp evaluations for each group were made after the 3rd, 5th and 7th washes, rated on a 1-10 scale as described above and plotted as a fitted regression line for each group vs. the baseline values obtained after the control washings.

Scalp changes are shown in Table 1. The more negative the change, the better the improvement of the scalp condition.

TABLE 1

<u>SHAMPOO</u>	<u>ITCHING</u>	<u>IRRITATION</u>	<u>DRYNESS</u>	<u>FLAKING</u>
<u>CONCLUSION</u>				
PANTENE	-0.28	-0.35	-0.28	-1.75
				marginally effective

	H&S	0.18	-0.28	1.05	-2.05	marginally effective
5	Form B	-2.10	-0.15	-3.93	-5.30	most effective
	Form A	-1.25	-1.00	-1.00	-3.72	effective

10 These results show that the products of the present invention are considerably more effective than leading commercial anti-dandruff shampoos (which contain anionic surfactant as the major surfactant component) in reducing or substantially eliminating scalp disorder factors occasioned by the use of an irritating, high anionic content shampoo.

15 The remaining two groups of 15 panelists each (Group E and F) were subjected to a different protocol. In this protocol, there were no control washings, but instead the hair of each panelist was washed every other day by the washing procedure described above (for a total of 14 washings) with HEAD AND SHOULDERS™ (Group E) and with Formula B (Group F). The objective of this protocol was to determine the effectiveness of each product to prevent the onset of scalp disorders. As above, a baseline evaluation of scalp disorder for each panelist prior to the 14 washings was established by dermatological observation and panelist input.

30 Changes in scalp characteristics after 14 washes rated on a 1-10 scale were plotted as above. Results are shown in Table 2.

TABLE 2

35	<u>SHAMPOO</u>	<u>ITCHING</u>	<u>IRRITATION</u>	<u>DRYNESS</u>	<u>FLAKING</u>	<u>CONCLUSION</u>
	H and S	-2.42	-0.07	0.08	-2.98	marginally effective
40	Form B	-2.69	-1.49	-4.93	-4.84	effective

The results show that the product of the invention is considerably more effective in preventing the onset of scalp disorder problems than a leading commercial brand.

Again, it is believed that the major factor contributing to this efficacy is the mild surfactant system present in the formulations of this invention.

5 An additional feature of the invention is based on the discovery that mild conditioning shampoos of the invention which contain an alkyl, alkaryl or alpha olefin sulfonate as the main anionic surfactant and a combination of climbazole and salicylic acid or  
10 acetylsalicylic acid also provide improved conditioning effects in an acid shampoo (pH 4.0-5.0). Two shampoo formulations containing the following surfactant and therapeutic ingredient compositions were prepared:

15		<u>Example 3</u>	<u>Example 4</u>
	Climbazole	1.5	--
	Salicylic Acid	2.0	--
	Sodium AOS (40%)	22.5	22.5
20	Na Cumene Sulfonate (43.3%)	7.0	7.0
	Cocoamidopropyl Betaine (30%)	30.0	30.0

The remainder of each formulation was identical and essentially as described Examples 1 and 2. The pH of  
25 each formula was adjusted to 4.0 using citric acid.

Hair washed with the shampoo of Example 3 exhibited improved combability as compared with hair washed using the Example 4 formulation. This is indicative of an  
30 increased deposition on the hair of the cationic hair conditioning components present in the formula of Example 3 as a result of the presence of the therapeutic agents climbazole and salicylic acid.

35 In another embodiment of the invention, skin care products in the form of gels, lotions, creams, foams, bar and liquid soaps containing one or more sebum-promoting active ingredients are provided which are adapted to be applied to areas of the skin other than the scalp as skin

moisturizers. It has been found that the active ingredients climbazole, selenium sulfide and zinc pyrithione tend to stimulate the sebaceous glands when rubbed into the skin, thereby promoting the natural production of oily sebum by the body. The excess sebum generated in the skin acts as a natural skin softener and moisturizer. These products and similar products such as triclosan, ketoconazole, piroctone olamine and their mixtures thereof, may be formulated to contain from about 0.1 to about 5% by weight, more preferably from about 0.25 to 2.5% by weight of the active ingredient, dispersed or dissolved in a suitable carrier medium which may comprise water, lower C<sub>1</sub> to C<sub>4</sub> alcohols such as ethanol or isopropanol, polyalcohols such as glycerine or propylene glycol, and mixtures thereof.

These carrier compositions may also contain one or more surfactants, e.g., anionic, cationic, non-ionic or amphoteric surfactants such as to form a cleansing lotion; one or more soap materials such as sodium tallowate, sodium cocoate, sodium palm kernelate or sodium palmitate such as used to formulate a bar soap; thickening agents such as carboxymethyl cellulose used to form a gel; and softeners, emollients, fatty acids, fatty alcohols, fatty acid esters, natural or synthetic oils or waxes and suspending agents such as used to formulate skin creams, lotions and emulsions. These products may also contain dyes, perfumes, preservatives and pH regulating agents.

Tests were performed using two different skin cleansing creams, one containing 1.0 wt% climbazole and the other containing 2.0 wt% zinc pyrithione. These products were rubbed into dry skin areas of two groups of panelists, each of whom complained of skin dryness, for a period of one minute each and once a day for 7 days. Sebumeter readings taken at the end of the test period showed an increase in skin sebum content. A consequent decrease in

skin dryness and cracking was also observed in the panelists.

CLAIMS

What is claimed is:

5           1. A mild, aqueous detergent composition having a therapeutic effect on skin disorders comprising:

(a) from about 4 to about 12% by weight of anionic surfactant;

10

(b) amphoteric surfactant present in said composition at a level of at least about 0.75 parts by weight per part by weight of said anionic surfactant; and

15

(c) an effective amount of a therapeutic agent selected from the group consisting of 1-imidazolyl-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one (climbazole);  
20 acetylsalicylic acid; salicylic acid; 2,4,4'-trichloro-2'-hydroxy diphenyl ether (triclosan); 1-acetyl-4-(4-(2-(2,4-dichlorophenyl)-2-(1H-imidazolyl-1-methyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-piperazine  
25 (Ketoconazole); 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone monoethanolamine salt (piroctone olamine); selenium sulfide, zinc pyrithione; coal tar; sulfur; 2-(4'-isobutylphenyl) propionic acid (ibuprofen) and  
30 mixtures thereof.

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30

2. The composition of claim 1 containing from about 0.75 to 1.25 parts by weight of amphoteric surfactant per part by weight of anionic surfactant.

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3. The composition of claim 2 containing from about 0.9 to 1.1 parts by weight of said amphoteric surfactant per part by weight of anionic surfactant.

4. The composition of claim 1 wherein said detergent composition is a shampoo.

5 5. The composition of claim 4 wherein said therapeutic agent is climbazole present at a level of from about 0.1 to about 4% by weight.

10 6. The composition of claim 5 wherein said climbazole is present at a level of from about 0.25 to about 2.5% by weight.

15 7. The composition of claim 5 wherein said therapeutic agent comprises a mixture of climbazole and salicylic acid wherein said salicylic acid is present at a level of from about 0.1 to about 10% by weight.

20 8. The composition of claim 7 wherein said salicylic acid is present at a level of from about 0.25 to about 2.5% by weight.

9. The composition of claim 4 wherein said amphoteric surfactant is a betaine or sulfobetaine.

25 10. The composition of claim 9 wherein said betaine is cocoamidoethyl betaine or cocoamidopropyl betaine.

30 11. The composition of claim 4 wherein said anionic surfactant is selected from the group consisting of the sodium or ammonium C<sub>10</sub> to C<sub>18</sub> alkyl sulfates or sulfonates, C<sub>14</sub> to C<sub>18</sub> alpha olefin sulfonates, C<sub>8</sub> to C<sub>12</sub> alkyl polyethoxy sulfates and mixtures thereof, and mixtures thereof with an aryl sulfonate.

35 12. The composition of claim 2 wherein said anionic surfactant is present at a level of from about 6 to 10% by weight.

13. The composition of claim 4 further containing a hair conditioning agent selected from the group

consisting of organosilicone compounds, aminosilicones, water insoluble hydrocarbons, water insoluble fatty acid esters, quaternary ammonium salts and mixtures thereof, present at a level of from about 0.2 to 5% by weight.

5

14. The composition of claim 13 wherein said hair conditioner comprises a quaternary ammonium salt.

10

15. The composition of claim 14 wherein said therapeutic agent comprises a mixture of climbazole and salicylic acid.

15

16. The composition of claim 14 wherein said quaternary ammonium salt is selected from the group consisting of tricetyl methyl ammonium chloride, dicetyl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, tristearyl methyl ammonium chloride and mixtures thereof.

20

17. The composition of claim 13 wherein said conditioner is a polysiloxane or aminopolysiloxane.

25

18. The composition of claim 13 wherein said quaternary ammonium salt is the salt of a polymer of dimethyl ammonium chloride or copolymers thereof with acrylamide.

30

19. The composition of claim 4 further containing one or a mixture of suspending agents present at a level of from about 0.5 to 7% by weight.

35

20. The composition of claim 19 wherein said suspending agent is a long chain alcohol or ethoxylated alcohol averaging about 26 to 40 carbon atoms.

21. A method of treating or preventing scalp disorders such as irritation, inflammation, dryness, redness and itching comprising applying to the hair and scalp an aqueous composition comprising:



(a) from about 4 to about 12% by weight of anionic surfactant;

5 (b) amphoteric surfactant present in said composition at a level of at least about 0.75 parts by weight per part by weight of said anionic surfactant; and

10 (c) an effective amount of a therapeutic agent selected from the group consisting of 1-imidazolyl-1-(4-chlorophenoxy)-3,3-dimethylbutan-2-one (climbazole);  
15 acetylsalicylic acid, salicylic acid, 2,4,4'-trichloro-2'-hydroxy diphenyl ether (triclosan); 1-acetyl-4-(4-(2-(2,4-dichlorophenyl)-2-(1H-imidazolyl-1-methyl)-1,3-dioxolan-4-yl)methoxy)phenyl)-piperazine  
20 (Ketoconazole); 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone monoethanolamine salt (piroctone olamine); selenium sulfide, zinc pyrithione; coal tar; sulfur; 2-(4'-isobutylphenyl) propionic acid (ibuprofen) and mixtures thereof.

25

22. The method according to claim 21 wherein the composition contains from about 0.75 to 1.25 parts by weight of amphoteric surfactant per part by weight of anionic surfactant.

30

23. The method according to claim 22 wherein the composition contains from about 0.9 to 1.1 parts by weight of said amphoteric surfactant per part by weight of anionic surfactant.

35

24. The method according to claim 21 wherein said therapeutic agent is climbazole present at a level of from about 0.1 to about 4% by weight.

25. The method according to claim 24 wherein said climbazole is present at a level of from about 0.25 to about 2.5% by weight.

5           26. The method according to claim 24 wherein said therapeutic agent comprises a mixture of climbazole and salicylic acid wherein said salicylic acid is present at a level of from about 0.1 to about 10% by weight.

10           27. The method according to claim 26 wherein said salicylic acid is present at a level of from about 0.25 to about 2.5% by weight.

15           28. The method according to claim 21 wherein said amphoteric surfactant is a betaine or sulfobetaine.

20           29. The method according to claim 28 wherein said betaine is cocoamidoethyl betaine or cocoamidopropyl betaine.

25           30. The method according to claim 21 wherein said anionic surfactant is selected from the group consisting of the sodium or ammonium C<sub>10</sub> to C<sub>18</sub> alkyl sulfates or sulfonates, C<sub>14</sub> to C<sub>18</sub> alpha olefin sulfonates, C<sub>8</sub> to C<sub>12</sub> alkyl polyethoxy sulfates and mixtures thereof, and mixtures thereof with an aryl sulfonate.

30           31. The method according to claim 22 wherein said anionic surfactant is present at a level of from about 6 to 10% by weight.

35           32. The method according to claim 21 wherein the composition further contains a hair conditioning agent selected from the group consisting of organosilicone compounds, aminosilicones, water insoluble hydrocarbons, water insoluble fatty acid esters, quaternary ammonium salts and mixtures thereof, present at a level of from about 0.2 to 5% by weight.

33. The method according to claim 32 wherein said hair conditioner comprises a quaternary ammonium salt.

5 34. The method according to claim 33 wherein said therapeutic agent comprises a mixture of climbazole and salicylic acid.

10 35. The method according to claim 33 wherein said quaternary ammonium salt is selected from the group consisting of tricetyl methyl ammonium chloride, dicetyl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, tristearyl methyl ammonium chloride and mixtures thereof.

15 36. The method according to claim 32 wherein said conditioner is a polysiloxane or aminopolysiloxane.

20 37. The method according to claim 33 wherein said quaternary ammonium salt is the salt of a polymer of dimethyl ammonium chloride or copolymers thereof with acrylamide.

25 38. The method according to claim 21 wherein the composition further contains one or a mixture of suspending agents present at a level of from about 0.5 to 7% by weight.

30 39. The method according to claim 38 wherein said suspending agent is a long chain alcohol or ethoxylated alcohol averaging about 26 to 40 carbon atoms.

35 40. A method for treating dry skin conditions comprising rubbing into affected skin areas other than the scalp a skin care composition containing a carrier having dispersed therein an agent that stimulates the sebaceous glands to promote the production of oily sebum selected from the group consisting of 1-imidozoyl-1-(4-chlorophenoxy)-3,3- dimethylbutane-2-one; 2,4,4'-trichloro-2'- hydroxy diphenyl ether; 1-acetyl-4-(4-(2-

(2,4-dichlorophenyl)-2-(1H-imidazolyl-1-methyl)-1,3-dioxolan-4-yl)methoxy) phenyl)-piperazine; 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone monoethanolamine salt; selenium sulfide and zinc pyrithione, said moisturizing agent present in said composition in an amount effective to promote the natural secretion of sebum in the skin.

41. The method according to claim 40 wherein said skin care composition contains from about 0.1 to about 5% by weight of said agent.

42. The method according to claim 41 wherein said agent is zinc pyrithione or 1-imidazol-1-(4-chlorophenoxy)-3,3-dimethylbutane-2-one.

43. The method according to claim 42 wherein said skin care composition contains from about 0.25 to 2.5% by weight of said moisturizing agent.

44. The method according to claim 40 wherein said skin care composition is in the form of a cleansing lotion, gel, bar soap, liquid soap, foam, cleansing liquid or skin cream.

# INTERNATIONAL SEARCH REPORT

International Application No  
PC 1/US 96/03821

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K7/50 A61K7/06 A61K7/48

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 6 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)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 210 774 (SHIONOGI & CO. LTD) 4 February 1987  see the whole document ---	1-4, 9-14,17, 18, 21-23, 28-33, 36,37
X	US,A,4 329 334 (D. T. SU) 11 May 1982  see the whole document ---  -/-	1,2,4-6, 9-12, 19-22, 24,25, 28-31, 38,39

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search  2 August 1996	Date of mailing of the international search report  13.08.96
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  Sierra Gonzalez, M

# INTERNATIONAL SEARCH REPORT

International Application No.

PC1/US 96/03821

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