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(54) Title: COMPOSITIONS AND METHODS FOR THE MANAGEMENT OF HYPERPROLIFERATIVE DERMATOLOGICAL CONDITIONS

(57) Abstract: The invention describes compositions and methods for the management of hyperproliferative skin conditions such as psoriasis. The preferential composition contains a natural leukotriene inhibitor selected from Boswellia serrata gum resin, its extractives, isolates or derivatives in combination with a bioavailable organic selenium nutritional supplement. These compositions are administered orally and topically to the individual human or animal in need of treatment at optimal levels to manifest the desired benefits, with no untoward side effects.
Description

Compositions and methods for the management of hyperproliferative dermatological conditions

Technical field

[0001] The invention is related to compositions and methods for the management of hyperproliferative skin conditions such as psoriasis, and their associated symptoms. The compositions described herein contain a natural leukotriene inhibitor selected from Boswellia serrata gum resin, its extractives, isolates or derivatives in combination with a bioavailable organic selenium nutritional supplement. These compositions are administered orally and topically to the individual human or animal in need of treatment at optimal levels and in suitable dosage forms to manifest the desired benefits, with no untoward side effects.

Background art

[0002] Psoriasis is a chronic skin disease marked by periodic flare-ups of sharply defined red patches covered by a silvery, flaky surface. In psoriasis the skin epidermis is subjected to destructive changes due to genetic abnormalities in the immune system that are triggered by stress and environmental factors. There is hyperproliferation of immature keratinocytes in the epidermis, forming patches or plaques with silvery, flaky dead skin shed from the surface. In the dermis, the blood vessels provide an increased blood supply to the abnormally multiplying
keratinocytes, causing the underlying inflammation and redness
characteristic of psoriasis. Several types of psoriasis exist occurring
independently, concurrently or consequentially. The most common form of
psoriasis is plaque psoriasis. Psoriatic arthritis is a debilitating disorder
that includes both psoriasis and arthritis.

[0003] Psoriasis is clinically addressed with topical medications, phototherapy,
systemic medications. Agents such as steroidal drugs, cyclosporine,
Methotrexate, oral and topical retinoids, selenium sulfide used in
pharmaceutical preparations for this purpose have various side effects.
There is no known cure for psoriasis.

[0004] Boswellia serrata (Roxb.) Burseraceae is a large tree which grows in the
dry and hilly parts of India. The exudate of Boswellia serrata is a gum resin
commonly known as "Dhup", "Indian Frankincense"or "Indian
Olibanum"(Anonymous, 1948 and Chopra et al, 1956), The gum resin
known as Salai Guggal has been used in Ayurvedic system of medicine for
the treatment of rheumatism, respiratory diseases and liver disorders
(Kirtikar and Basu, 1935). Ancient Ayurvedic texts (Shushrutha Samhitha
Gulabkunvarba,1949) and Charaka Samhitha (Chowkhamba,1968)
mentioned the anti-rheumatic activity of guggals. The nonacidic oil fraction
of gum resins of Boswellia was found to exhibit significant pain relieving
effects in rats (Menon and Kar, 1971 and Menon and Kar, 1969). The
acidic fraction of gum Boswellia serrata, containing boswellic acids, was
found to exhibit antipyretic action in rats and rabbits (Singh and Atal, 1986, Singh et al., 1993). The acidic fraction of gum Boswellia serrata, however, was not known to have any analgesic property. In nature, boswellic acids occur in the gum or exudate from the tree Boswellia serrata (Roxb.). The gum contains a mixture of four boswellic acids.

[0005] Boswellic acids inhibit 5-lipoxygenase (Safayhi et al., 1992) the enzyme which catalyzes conversion of arachidonic acid to inflammatory leukotrienes. Boswellic acids also inhibit the enzyme human leukocyte elastase (HLE) which catalyzes connective tissue break down (Safayhi et al., 1997).

[0006] Inflammatory leukotrienes have been implicated in the pathogenesis and pathophysiology of psoriasis. In lesional skin from psoriasis and eczema patients, leukotriene B4 was found to increase by approximately 6.6-fold (Reilly et al. 2000). A 5-lipoxygenase catalyzed product from arachidonic acid, leukotriene B4, is considered to play a significant role in the pathogenesis of psoriasis (Iversen et al., 1997). A massive increase in human leukocyte elastase (HLE) activity was found in lesional skin of psoriasis (31 times), allergic contact dermatitis (55 times), and atopic dermatitis (35 times), but not in uninvolved skin of diseased patients (Wiedow, 1992).

[0008] WO 97/07796 describes the use of boswellic acid and its derivatives for inhibiting normal and increased leukocytic elastase or plasmin activity.

[0009] US 5,888,514 describes a natural composition containing boswellic acids for treating bone or joint inflammation.


[0013] EP 0552657 describes the use of pure boswellic acid, a physiologically acceptable salt, derivative, or a salt of the derivative or a boswellic acid containing herbal preparation for the prophylaxis and/or control of inflammatory processes caused by increased leukotriene formation in human and veterinary medicine.

[0014] WO 00/57893 describes compositions containing Boswellia serrata extract wherein Boswellia serrata extract, boswellic acid or a derivative thereof is useful in preparing skin care or hair care compositions with the ability to provide a soothing effect to irritated skin.

[0015] Selenium is a vital trace element nutrient with multiple roles in the growth and functioning of living cells in higher animals and humans. At the molecular level, selenium (as selenocysteine) is an essential component of
the active sites of the antioxidant enzyme glutathione peroxidase, and the enzymes participating in thyroid functions iodothyronine-5'-deiodinase and mammalian thioredoxin reductase. Selenium is also present in several other mammalian selenoproteins. Low selenium status has been linked with the occurrence of decreased immunity to diseases and the prevalence of various forms of cancer.

[0016] Patients with moderate or severe psoriasis have been shown to have low blood selenium levels and increased levels of malondialdehyde, a product of free radical induced oxidation (Corrocher, et al. 1989). Low selenium dietary intake has been linked to the progression of psoriasis in a clinical study (Serwin, et al. 1999). It has been demonstrated in both human subjects and experimental animals that topical selenomethionine reduces the degree of damage to the skin induced by UV radiation (Burke, et al., 1992). The antioxidant action of selenomethionine through its role in the antioxidant enzymes (Cronin, 2000) may therefore help in cases of psoriasis.

[0017] Recent studies suggest that that psoriasis is not primarily a skin disorder but an immunological disturbance under the skin. The skin manifestations are a result of overstimulation of superficial skin cells (Langerhans cells) due to increased production of interleukin 2, 6 and 8 as well the diminished production of transforming growth-factor-alpha Interleukin-10 (Christ, 1999)
[0018] The effect of Selenium supplementation (400 micrograms/day for 6 weeks as Se-yeast, containing about 70% selenomethionine) on skin and blood Se-content, on skin glutathione peroxidase activity and on various chemical and immunological parameters of blood and skin was investigated in 7 psoriatic patients. The results of this study suggested that selenomethionine may be able to modulate the immunological mechanism of psoriatic lesions by increasing the number of CD4+ T cells (Harvima, 1993).

[0019] Tumor necrosis factor-alpha (TNF-alpha) and its receptors play important roles in the induction and maintenance of psoriatic lesions. A recent study reports that oral supplementation with selenomethionine was ineffective as adjuvant treatment in plaque psoriasis and may contribute to the maintenance of elevated TNF-R1 (soluble TNF-alpha receptor type 1) concentration in psoriasis patients despite the remission of skin lesions. (Serwin et al., 2003)


[0021] WO02096429 describes an agent for the external therapy of psoriasis in the form of liposomal emulsions of preparations of methylxathine group, selenium and some other preparations are used as active substances.

[0022] IT1244459 describes Pharmaceutical compositions which can be administered topically for the treatment of skin diseases such as vitiligo,
acne, psoriasis, alopecia, hypotrichosis, comprising one or more oils of
animal origin selected from cod liver oil, mink oil and tortoise oil containing
lithium, zinc, copper and possibly gold, silver, sulphur, selenium and
silicon dissolved or dispersed in them are described.

and selenium, as a selenoamino acid or selenium yeast extract and an
epidermal growth factor in a topical carrier and method of using the
composition to reduce and repair skin damage, resulting from aesthetic
(exfoliation and chemical peels) and surgical (laser and other therapies)
procedures and other chemical and thermal burns to the cutaneous
tissues.

[0024] None of the prior art cited above addresses psoriasis with a natural dual
inhibitor of 5-lipoxygenase and human leukocyte elastase in combination
with organic selenium supplement. The anti-complementary activity of
boswellic acids is detailed in literature (Kapil, A et al. 1992). The
complement-dependent induction of TNF-alpha is a well-established
pathway. Therefore the combination treatment of the current invention
would prevent any potential elevation of TNF-alpha levels not addressed
by selenium supplementation.

[0025] The following is a list of literature cited in this application, each of which is
hereby incorporated by reference in its entirety:


Disclosure of the Invention

[0047] Hyperproliferative skin disorders are exemplified by psoriasis. Psoriasis is a chronic skin disease characterized by periodic flare-ups in the form of red patches covered by a silvery, flaky surface that appear on the skin. It is attributed to genetic abnormalities in the immune system that are triggered by environmental factors, and therefore classified as an autoimmune disorder. There are several variants of psoriasis of which plaque psoriasis is the most common and is seen on the elbows, knees and lower back. In psoriatic arthritis, psoriatic lesions are accompanied by symptoms of arthritis. Psoriatic arthritis is characterized by stiff, tender, and inflamed joints.

[0048] The current invention addresses hyperproliferative skin conditions with a novel treatment regimen in which a natural dual acting inhibitor of 5-lipoxygenase and human leukocyte elastase is ingested orally, as well as applied topically, in combination with a bioavailable organic selenium supplement which is ingested orally.
[0049] The processes leading to all autoimmune disease involve the human leukocyte antigen (HLA) system, which is genetically regulated. Malfunction of this system is at the root of most immune disorders, including psoriatic arthritis. The current invention is directed towards supplying nutrients that would potentially inhibit the inflammatory process through inhibiting the expression of pro-inflammatory enzymes and modulating the expression of keratinocyte growth factor. Successful treatment entails configuring the correct dosing regimen that would favorably influence the underlying genetic processes involved.

**Brief Description of Drawings**

[0050] Figure 1 shows the appearance of psoriatic lesions in patient 1, patient 2, patient 3 initially, at the end of week 8 (visit 1) and the end of week 12 (visit 2) during treatment.

[0051] Figure 2 shows the appearance of psoriatic lesions in patient 4, patient 5, patient 6 initially, at the end of week 8 (visit 1) and the end of week 12 (visit 2) during treatment.

[0052] Figure 3 shows the appearance of psoriatic lesions in patient 7, patient 8, patient 9 initially, at the end of week 8 (visit 1) and the end of week 12 (visit 2) during treatment.

[0053] Figure 4 shows the appearance of psoriatic lesions in patient 10, patient 11, patient 12 initially, at the end of week 8 (visit 1) and the end of week 12 (visit 2) during treatment.
Mode(s) for carrying out the invention

[0054] Exemplary embodiments of the current invention present compositions and dosing regimens to effect successful treatment of psoriasis.

[0055] Example 1 Compositions of the Invention

[0056] An exemplary embodiment of the active ingredient composition of the oral formulation of the invention is presented in Table 1.

<table>
<thead>
<tr>
<th>Active Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-boswellic acid</td>
<td>64 mg</td>
</tr>
<tr>
<td>Acetyl-beta-boswellic acid</td>
<td>48 mg</td>
</tr>
<tr>
<td>11-keto-beta-boswellic acid</td>
<td>24 mg</td>
</tr>
<tr>
<td>Acetyl-11-keto-beta-boswellic acid</td>
<td>32 mg</td>
</tr>
<tr>
<td>L(+)-Selenomethionine (trituration in</td>
<td>20 mg</td>
</tr>
<tr>
<td>Dicalcium phosphate)</td>
<td></td>
</tr>
</tbody>
</table>

[0058] The formulation is prepared in the form of a capsule, tablet, power, spansule or other dosage form for oral administration, with commonly used excipients and additives for such purposes.

[0059] An exemplary embodiment of the formulation for topical application is presented in Table 2.
Table 2: Composition of the topical cream

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>% (w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purified water</td>
<td>60.000</td>
</tr>
<tr>
<td>Carbowax 940</td>
<td>0.250</td>
</tr>
<tr>
<td>Glycerin</td>
<td>4.000</td>
</tr>
<tr>
<td>Methylparaben</td>
<td>0.200</td>
</tr>
<tr>
<td>Edetate sodium</td>
<td>0.010</td>
</tr>
<tr>
<td>Cetyl alcohol</td>
<td>3.500</td>
</tr>
<tr>
<td>Stearyl alcohol</td>
<td>3.500</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>6.500</td>
</tr>
<tr>
<td>Glycerol stearate</td>
<td>2.500</td>
</tr>
<tr>
<td>PEG-400 stearate</td>
<td>2.500</td>
</tr>
<tr>
<td>Isopropyl palmitate</td>
<td>6.000</td>
</tr>
<tr>
<td>Vitamin E acetate</td>
<td>1.000</td>
</tr>
<tr>
<td>Dimethicone</td>
<td>0.100</td>
</tr>
<tr>
<td>Propylparaben</td>
<td>0.100</td>
</tr>
<tr>
<td>Vitamin A palmitate</td>
<td>0.100</td>
</tr>
<tr>
<td>Ascorbyl palmitate</td>
<td>0.200</td>
</tr>
<tr>
<td>Boswellin®</td>
<td>5.000</td>
</tr>
<tr>
<td>Purified water</td>
<td>2.000</td>
</tr>
<tr>
<td>Triethanolamine</td>
<td>0.400</td>
</tr>
<tr>
<td>Imiduria</td>
<td>0.300</td>
</tr>
</tbody>
</table>

[0061] Boswellin (a trademark of Sabinsa Corporation, NJ, USA) is a standardized Boswellia serrata gum resin extract containing beta-boswellic acid, acetyl-beta-boswellic acid, 11-keto-beta-boswellic acid and Acetyl-11-keto-beta-boswellic acid.

[0062] The active ingredient may be formulated as a cream, lotion, patch, gel or any other topical dosage form.

[0063] Example 2 Treatment of psoriatic human subjects with the composition and method of the invention

[0064] 12 patients (6 males and 1 female) 18-65 years of age, presenting with primary plaque and secondary scale manifested as annular, polycyclic, morbiliform lesions accompanied by itching, peeling of skin, and bleeding on scratching, participated in the study.
The patients were administered tablets containing 400 mg boswellic acids and 100 mcg of selenium in the form of L(+)-Selenomethionine orally and also treated with a topical cream containing 400 mg of boswellic acids.

The daily dose regimen followed was 1 tablet as above with topical application as above, thrice daily for 150 days. PASI score (Psoriasis Area Severity Index) which takes into account body surface area as well as erythema (redness), induration (thickness), and scaliness, was assessed at 4 week intervals. Serum biochemical parameters were similarly assessed.

Psoriasis affected parts of the body were photographed at the initiation of the study and at 4 week intervals.

The patients were followed up for another 30 days and showed improvement in symptoms of psoriasis with no untoward side effects.

The effects of the treatment on the external manifestations of psoriasis are photographically represented in Figures 1-4.
Claims


2. The composition and method of claim 1 wherein the hyperproliferative skin condition is psoriasis.

3. The composition of claim 1 contains a dual inhibitor of 5-lipoxygenase and human leukocyte elastase selected from Boswellia serrata gum resin, Boswellia serrata gum resin extract containing boswellic acids, isolated boswellic acids, synthetic boswellic acids, or derivatives, singly or in combination; and a bioavailable organic selenium nutritional supplement selected from selenomethionine, methylselenocysteine, selenium-enriched vegetable materials.

4. The composition of claim 1 is administered orally and topically to the human or animal subject in need of treatment.

5. The composition and method of claim 1 consists of a formulation of Boswellia serrata extract and selenomethionine administered orally, in combination with a formulation of Boswellia serrata extract applied topically.

6. The oral formulation of claim 5 contains 50-500 mg boswellic acids represented by one or more of the following groups: a) beta-boswellic acid, acetyl beta-boswellic acid, 11 keto beta-boswellic acid, acetyl-11-keto-beta-boswellic acid, as single entities or mixtures, b) Congeners or derivatives of beta-boswellic acid, acetyl beta-boswellic acid, 11 keto beta-boswellic acid,
acetyl-11-keto-beta-boswellic acid; singly or in combination; and 100mcg of selenium as selenomethionine.

7. The topical formulation of claim 5 contains 50-400 mg of boswellic acid represented by one or more of the following groups: a) beta-boswellic acid, acetyl beta-boswellic acid, 11 keto beta-boswellic acid, acetyl-11-keto-beta-boswellic acid, as single entities or mixtures, b) Congeners or derivatives of beta-boswellic acid, acetyl beta-boswellic acid, 11 keto beta-boswellic acid, acetyl-11-keto-beta-boswellic acid; singly or in combination.

8. The oral formulation of claim 5 contains 10-400 mg of acetyl-11-keto-beta-boswellic acid and 10-100 mcg of L(+)-Selenomethionine.


10. The oral formulation of claim 5 is a tablet, capsule, spansule, powder, or other dosage form.

11. The topical formulation of claim 5 is a cream, lotion, gel, patch, medicated oil, or other dosage form.

12. The topical formulation of claim 9 is suitable for application to the skin, scalp or nails.
Figure 1: Improvement in psoriasis lesions—Patient 1, Patient 2, Patient 3. Photographs show initial lesion and lesion appearance at 4 week intervals.
Figure 2: Improvement in psoriasis lesions—Patient 4, Patient 5, Patient 6. Photographs show initial lesion and lesion appearance at 4 week intervals.
Figure 3: Improvement in psoriasis lesions—Patient 7, Patient 8, Patient 9. Photographs show initial lesion and lesion appearance at 4 week intervals.
Figure 4: Improvement in psoriasis lesions—Patient 10, Patient 11, Patient 12. Photographs show initial lesion and lesion appearance at 4 week intervals

Fig. 4
INTERNATIONAL SEARCH REPORT

PCT/US04/33846

A. CLASSIFICATION OF SUBJECT MATTER
   IPC(7) : A01N 25/00, 65/00; A61K 38/00, 45/00
   US CL : 514/863, 2; 424/278.1, 725, 769
   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)
   U.S. : 514/863, 2; 424/278.1, 725, 769

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 practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category *</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 5,670,064 A (MONTES) 13 June 1972 (13.06.1972), claim 1.</td>
<td>1 and 2</td>
</tr>
<tr>
<td>X</td>
<td>US 5,336,506 A (MAJEED et al.) 16 July 1996 (16.07.1996), see column 5, line 56 to column 7, line 55 and claims 1, 5, 6, 9-14, 16, 20, 21 and 24.</td>
<td>1-12</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

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“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search
22 November 2005 (22.11.2005)

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Date of mailing of the international search report
29 DEC 2005

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Form PCT/ISA/210 (second sheet) (April 2005)
Continuation of B. FIELDS SEARCHED Item 3:
USPat, USPgPub, EPO, JPO, Derwent, medline

search terms: boswellia serrata, boswellin, selenomethionine, selenium methionine, hypoproliferative skin, psoriasis