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(54) **Title**: TREATMENT OF PAIN AND/OR INFLAMMATION AND TREATMENT AND PREVENTION OF A SKIN OR MUCOSAL DISEASE AND/OR CONDITION

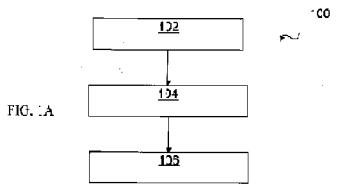

FIG. 1A

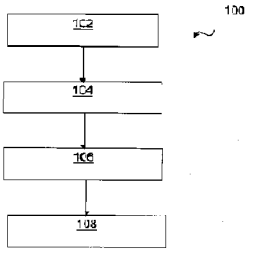

FIG. 1B

(57) **Abstract**: The invention discloses a composition for treating pain and/or inflammation and for treating a skin or mucosal disease or condition comprising menthol, ginseng and an emollient. The invention also discloses a method for treating pain and/or inflammation or for treating a skin or mucosal disease or condition. The invention additionally discloses use of the composition in the manufacture of a medicament for treatment of pain and/or inflammation or for treatment of a skin or mucosal disease. The invention further discloses a composition for treating a skin disease and/or a skin condition comprising one or more stabilised alpha hydroxyl acid. Also disclosed are methods for preventing and/or treating a skin disease or skin condition including the steps of: treating an area of skin with one or more composition according to the invention; applying one or more photosensitizer to the area of skin; and exposing the area of skin to light to thereby prevent and/or treat the skin disease and or condition.

WO 2010/127411 A1

TITLE

TREATMENT OF PAIN AND/OR INFLAMMATION AND TREATMENT AND PREVENTION OF A SKIN OR MUCOSAL DISEASE AND/OR CONDITION

FIELD OF THE INVENTION

The present invention relates to treating pain and/or inflammation. In particular, but not exclusively, the present invention relates to treating pain and/or inflammation associated with a dermatological method. The present invention also relates to a composition and photodermatological method for preventing and/or treating a skin or mucosal disease and/or condition.

BACKGROUND TO THE INVENTION

Despite recent advances in the treatment of pain and/or inflammation, many people complain that current treatments and methodologies are insufficient and that they experience significant pain and/or inflammation. Accordingly, there remains a need for alternative treatments for pain and/or inflammation.

One common type of ailments which cause significant pain are skin diseases and skin conditions. Additionally, some skin diseases and conditions such as, actinic keratosis (AK) can progress to more serious disease such as, skin cancer.

Cryotherapy remains one of the most common treatments for AK, but has a number of limitations. There has even been uncertainty as to the

duration one needs to freeze AKs to obtain maximal effect without excessive side effects. Common medical usage has recently demonstrated that a freeze of 6 to 20 seconds per lesion may be optimal.[1] However, this study did not look at long term efficacy of treatment.

Most studies of efficacy in management of AKs use lesion count as the means of quantifying effect. This has its limitations. In a large Australian study[2] it was demonstrated that AKs can come and go of their own accord. Managing specific lesions might not lead to an overall improvement in actinic disease.

While clinicians once focused on treating individual lesions, studies[2-4] suggest we should be increasingly managing the whole skin field rather than individual lesions. Treating one active AK may not assist any adjacent severely sun damaged skin. So treatments for field cancerization[4] have been more recently explored. Clinicians are moving away from lesion treatments in favour of treatments for the whole sun affected regions. Most commonly, the face, scalp, hands and forearms have been identified as regions in need of considering field treatment.

Other product classes promise new approaches to field treatments. These are becoming increasingly popular and include topical imiquimod[5] (IMIQ), topical 5-fluorouracil[6] (5FU), topical diclofenac[7] and photodynamic therapy[8] (PDT).

Lehmann recently compiled a literature review[9] of PDT for AKs. Complete response rates (CRRs) using Methyl aminolaevulinate PDT (MAL-PDT) for AKs range from 69% to 93% at 3 months. This non-invasive

treatment option was associated with minimal risk of scarring. Systemic uptake of MAL is negligible and the local phototoxic reactions that often occur during treatment rapidly heal to produce excellent cosmetic results. The side-effects of therapy, which are predominantly local phototoxic effects such as, burning, stinging and prickling sensations, are of mild-to-moderate intensity, of short duration and easily managed. Lehmann concluded that overall, the efficacy and low risk of side-effects afforded by this therapy have resulted in high patient preference in clinical trials.

In a recent randomized controlled trial (RCT), Kaufmann[10] performed an intra-individual, right-left comparison with MAL-PDT and cryotherapy on either side of the body. 121 patients with 1343 lesions (98% located on the extremities and the remainder on the trunk and neck) were included. Both treatments provided a high mean percentage reduction in lesion count at week 24 with: 78% for MAL-PDT and 88% for cryotherapy (P=0.002). Investigator's assessment of cosmetic outcome was significantly better for MAL-PDT than cryotherapy (P<0.001). Cosmetic outcome achieved by MAL-PDT compared with cryotherapy was also preferred by patients (50% vs. 22%, respectively, P<0.001). Both treatment regimens were safe and well tolerated.

WO 03/099283, the publication of PCT/US03/14486, teaches that 5-aminolaevulinic acid (ALA) may be used as a photosensitizing agent during treatments such as PDT.

Moloney[11] recently reported another RCT in which MAL and 5-aminolaevulinic acid (ALA) PDT were found to be both effective treatment

options for AKs. MAL is significantly more expensive than ALA. Sixteen male patients with scalp AK were randomized into a double-blind, split-scalp prospective RCT. Two treatment fields were defined (right and left frontoparietal scalp) and treated 2 weeks apart. These fields were randomized to receive either MAL or ALA as first or second treatment. MAL cream was applied for 3 hr; 20% ALA cream was applied for 5 hr. Both arms had similar AK reduction count. Discomfort post-procedure persisted for longer following treatment with ALA when compared with MAL-PDT (P = 0.044).

Other treatment options for AK include topical administration of clotrimazole as taught in WO 96/33714, the publication of PCT/US96/05554, and topical application of a formulation containing 2-methyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as taught in WO 2006/099275, the publication of PCT/US2006/008868.

Perrett[12] recently studied the management of AKs in post transplant patients. Eight organ transplant recipients with epidermal dysplasia were recruited to an open-label intra-patient RCT. Treatment with two cycles of topical MAL PDT one week apart was randomly assigned to one skin area, and 5-FU cream was applied twice daily for three weeks to a clinically and histologically comparable area. PDT was more effective than 5-FU in achieving complete resolution: eight of nine lesional areas cleared with PDT (CRR 89%, 95% CI: 0.52-0.99), compared with one of nine lesional areas treated with 5-FU (CRR 11%, 95% CI: 0.003-0.48) (P = 0.02). Cosmetic outcome and patient preference were also superior in the PDT-treated

group.

Tierney[13] mailed a questionnaire to 45 patients who had received PDT for AKs in 2005-2006. A total of 39 of the 45 patients participated (86.7%). A patient's reported recovery time was significantly more likely to be one week or less for PDT when compared with cryotherapy ($p = 0.02$) and surgical excision ($p = 0.02$). Borderline significance was found for the improved cosmetic outcome in PDT vs. surgical excision ($p = 0.058$) and for patient satisfaction with PDT compared with 5-FU ($p = 0.058$). Patients significantly preferred PDT to 5-FU ($p<0.001$) or imiquimod (IMIQ) ($p = 0.031$). PDT was found to have equivalent or improved recovery times, cosmetic outcomes, patient satisfaction and preference as a treatment for AKs by patients compared with other options.

In a suite of trials that investigated various light sources for PDT, Babilas[14-16] has demonstrated that intermittent light used to activate PDT can result in less pain than a constant light. Wiegell[17] has demonstrated that pain suffered during PDT can also be reduced by using a less intense light source.

US patents do not constitute common general knowledge in Australia or other countries. Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of the common general knowledge in the field.

OBJECT OF THE INVENTION

It is an object of the invention to provide a method and/or composition

for treating pain and/or inflammation. A preferred object is to treat pain and/or inflammation associated with a photodermatological method.

Another preferred object is to provide a photodermatological method and composition for preventing or treating a skin or mucosal disease and/or condition.

It is also a preferred object of this invention to overcome and/or alleviate one or more of the above disadvantages of the prior art and/or provide the consumer with a useful or commercial choice.

Further objects will be evident from the following description.

SUMMARY OF THE INVENTION

The present invention is broadly directed to treatment and prevention of pain and or inflammation. The treatment may be for acute inflammation and/or late phase response to a burn and/or other inflammatory stimuli. Although not limited thereto, the invention may be applied to dermatology and particularly to photodermatology. The present inventors have surprisingly discovered that a composition comprising menthol and ginseng treats and prevents pain and/or inflammation and treats skin and mucosal conditions and/or diseases. Additionally, the inventors have surprisingly discovered that a composition comprising one or more alpha hydroxy acid may normalize and/or stabilize skin and thereby improve efficacy of a photodermatological method. Further, the inventors have surprisingly discovered novel photodermatological methods and compositions which prevent and/or treat a skin or mucosal disease or

condition and which may then be associated with reduced pain and/or inflammation.

In a first aspect, which is not necessarily the only or broadest aspect, the invention resides in a composition for treating pain and/or inflammation and/or for treating a skin or mucosal disease or condition, the composition comprising menthol and ginseng.

The composition according to the first aspect may comprise menthol at a concentration of 0.1 to 5 %.

The composition according to the first aspect may comprise menthol at a concentration of 0.25 to 2.0 %.

The composition according to the first aspect may comprise menthol at a concentration of 0.4 to 0.6 %.

The composition according to the first aspect may comprise menthol at a concentration of 0.5%.

According to the first aspect the ginseng may be Panax ginseng (Asian ginseng) and/or *Panax quinquefolius* (American ginseng).

The Panax ginseng may be fresh ginseng, white ginseng, red ginseng or sun ginseng.

The ginseng may be present as an extract.

According to the first aspect the ginseng may be at a concentration of 1 to 10%.

According to the first aspect the ginseng may be at a concentration of 2.5 to 7.5 %.

According to the first aspect the ginseng may be at a concentration of

4 to 6 %.

According to the first aspect the ginseng may be at a concentration of 5 %.

According to the first aspect the composition may comprise one or more excipient.

The one or more excipient may be polysorbate 20.

According to the first aspect the composition may comprise one or more emollient.

The one or more emollient may be paraffin and/or aloe vera.

According to the first aspect the composition may further comprise an agent which helps seal disrupted inter-epithelial surfaces.

According to the first aspect the composition may further comprise a topical anaesthetic.

According to the first aspect the composition may further comprise one or more anti-inflammatory, one or more anti-histamine and or one or more anti-prostaglandin.

The anti-inflammatory may be an oral anti-inflammatory medication such as, fexofenidine, ceterizine or a non-steroidal anti-inflammatory drug (NSAID) such as, aspirin.

The above anti-inflammatory may also have some action on the neurokinin (NK1) and acetylcholine (ACH) receptors.

The anti-prostaglandin may be a non-steroidal anti-inflammatory such as aspirin, flunixin meglumine, dipyrone and phenylbutazone.

The composition may also comprise one or more medicament for

blocking a prostanoid such as, a NSAID such as, aspirin.

The ginseng may reduce a leukotriene. The leukotriene reduced may include leukotriene B4.

According to the first aspect the composition may further comprise a sunscreen.

In a second aspect the invention resides in a method for treating pain and/or inflammation and/or for treating a skin or mucosal disease or condition, the method including the step of applying the composition according to the first aspect to thereby treat the pain and/or inflammation.

In a third aspect, the invention resides in use of a composition according to the first aspect in the manufacture of a medicament for treatment of pain and/or inflammation and/or for the treatment of a skin or mucosal disease or condition.

The pain and/or inflammation treated according to the first, second and/or third aspect may be acute inflammation and/or late phase response to a burn and/or other inflammatory stimuli.

The pain and/or inflammation treated according to the first, second and/or third aspect may be associated with a photodermatological method.

The skin disease and/ or skin condition treated may selected from the group consisting of: actinic keratosis (AK); skin cancer; a pre-cancerous growth; a condition resulting from pre-emptive and/or post-testing for an allergy; sunburn; a skin disease or condition resulting from a radiotherapy treatment; a skin disease or condition resulting from a tattoo; urticaria; eczema and other forms of dermatitis; or a burn.

The mucosal disease or condition treated may be a cough; sinusitis; or post-chemotherapy bladder pain.

The composition may also be used to prepare skin for one or more procedure such as, PDT or a tattoo.

In a fourth aspect the invention resides in a composition for treating a skin disease and/or a skin condition comprising one or more alpha hydroxyl acid (AHA).

According to the fourth aspect the one or more AHA may be selected from the group consisting of glycolic acid, lactic acid, citric acid, malic acid, tartaric acid and mandelic acid.

According to the fourth aspect the one or more AHA is at a concentration in the range of 2 to 20%.

According to the fourth aspect the one or more AHA is at a concentration in the range of 5 to 15 %.

According to the fourth aspect the one or more AHA is at a concentration in the range of 8 to 12 %.

According to the fourth aspect the one or more AHA is at a concentration of 10 %.

According to the fourth aspect the one or more AHA is at a concentration of 5 %.

The one or more AHA may be stabilised.

In a fifth aspect the invention resides in a method for treating a skin disease or a skin condition including the step of applying a composition according to the fourth aspect to thereby treat the skin disease or skin

condition.

In a sixth aspect the invention resides in use of a composition according to the fourth aspect in the manufacture of a medicament for treatment of a skin disease or a skin condition.

In a seventh aspect, the invention resides in a method for preventing and/or treating a skin disease or skin condition including the steps of:

treating an area of skin with a composition according to the first aspect;

applying one or more photosensitizer to the area of skin; and

exposing the area of skin to light to thereby prevent and/or treat the skin disease and or condition.

The step of treating the area of skin with a composition according to the first aspect may be conducted prior to exposure to light, during exposure to light and/or after exposure to light.

The method of the seventh aspect may also include a step of treating the area of skin with a composition according to the fourth aspect. Preferably the step of treating the area of skin with a composition according to the fourth aspect is conducted prior to exposing the area of skin to light.

The one or more photosensitizer may be 5-aminolaevulinic acid.

The light may comprise two or more wavelengths.

The two or more light wavelengths may be blue light and red light.

The method may also include the step of treating with one or more co-therapeutic.

The one or more co-therapeutic may be 5-fluorouracil and/or

imiquinod.

The method may also be combined with one or more physical treatment.

The physical treatment may comprise cryotherapy and/or excision.

In an eighth aspect, the invention resides in a method for preventing and/or treating a skin disease or skin condition including the steps of:

treating an area of skin with a composition according to the fourth aspect;

applying one or more photosensitizer to the area of skin; and

exposing the area of skin to light to thereby prevent and/or treat the skin disease and or condition.

The method of the eighth aspect may also include a step of pre-treating the area of skin with a composition according to the first aspect.

The method of the eighth aspect may also include a step of treating the area of skin with a composition according to the first aspect during the exposure step.

The method of the eighth aspect may also include a step of post-treating the area of skin with a composition according to the first aspect.

The one or more photosensitizer may be 5-aminolaevulinic acid.

The light may comprise two or more wavelengths.

The two or more light wavelengths may be blue light and red light.

The method may also include the step of treating with one or more co-therapeutic.

The one or more co-therapeutic may be 5-fluorouracil and/or

imiquinod.

The method may also be combined with one or more physical treatment.

The physical treatment may comprise cryotherapy and/or excision.

In a ninth aspect the invention resides in a composition for treating a skin disease or a skin condition comprising an emollient, a topical anaesthetic and further comprising one or more further component selected from the group consisting of a pain reliever, an agent to help seal disrupted inter-epithelial surfaces and an agent to block noxious signalling from one or more receptor.

In a tenth aspect the invention resides in a method for treating a skin disease or a skin condition including the step of applying a composition according to the eighth aspect.

In an eleventh aspect the invention resides in use of a composition according to the ninth aspect in the manufacture of a medicament for treatment of a skin disease or skin condition.

According to the ninth, tenth and eleventh embodiments, the noxious signalling blocked may be noxious signalling from a receptor such as, the transient receptor potential vanilloid receptor 1.

In a twelfth aspect the invention resides in a composition comprising stabilized ALA.

In a thirteenth aspect the invention resides in a method for treating a skin disease or a skin condition including the step of applying a composition according to the twelfth aspect.

In a fourteenth aspect the invention resides in use of a composition according to the twelfth aspect in the manufacture of a medicament for treatment of a skin disease or skin condition.

In a fifteenth aspect the invention resides in a method for treating a skin disease or a skin condition including the step of exposing an area of skin to be treated to light of two discrete and different wavelengths.

The light may be blue light and red light.

Further features of the present invention will become apparent from the following detailed description.

In this specification, the terms "comprises", "comprising" or similar terms are intended to mean a non-exclusive inclusion, such that a method, system or apparatus that comprises a list of elements does not include those elements solely, but may well include other elements not listed.

BRIEF DESCRIPTION OF THE DRAWINGS

In order that the present invention may be readily understood and put into practical effect, reference will now be made to the accompanying illustrations wherein:

FIG. 1A is a flowchart showing a first embodiment of a method of the invention;

FIG. 1B is a flowchart showing an additional step in the method shown in FIG. 1A;

FIG. 1C is a flowchart showing a second embodiment of a method of the invention;

FIG. 1D is a flowchart showing an additional step in the method shown in FIG. 1C;

FIG. 2A is a photo showing a right hand side of a subject's face at initial consult;

FIG. 2B is a photo showing a left hand side of a subject's face at initial consult;

FIG. 2C is a photo showing a front-on view of a subject's face at initial consult;

FIG. 2D is a photo showing a right hand side of a subject's face ten weeks after receiving a second treatment according to the method of the invention;

FIG. 2E is a photo showing a left hand side of a subject's face ten weeks after receiving a second treatment according to the method of the invention;

FIG. 2F is a photo showing a front-on view of a subject's face ten weeks after receiving a second treatment according to the method of the invention;

FIGS. 2G and 2H are photos showing punch biopsy results of a subject treated according to the method of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates, at least in part, to relief of pain and/or inflammation. Although it will be explained with reference to photodermatology, aspects of the present invention may be applied to the general treatment of pain and/or inflammation.

Treatment of pain does not require complete cessation of pain and includes partial relief of pain.

A skin disease or condition includes damaged or unhealthy skin. Damaged skin includes skin damaged by the sun or other radiation as well as actinic keratosis. Treatment of a skin disease or condition includes pre-treatment of skin in preparation for a procedure such as, tattooing.

A mucosal disease or condition includes damaged or unhealthy mucosa.

Within the field means the area around prior skin damage or skin abnormalities such as, AKs, a lesion, pre-cancerous lesions and a cancer.

A photosensitizer is a chemical compound that can be excited by light. The light may be of a specific wavelength. This light may be visible or near-infrared light. A photosensitizer includes a metabolic precursor which is converted to a photosensitizer after application to a subject.

An emollient refers to a compound which softens skin. One or more emollient may be combined to form a moisturiser.

The present inventors have advantageously found that a composition comprising menthol and ginseng may treat pain and/or inflammation and/or treat a skin or mucosal condition or disease. The composition may treat acute inflammation and/or late phase response to a burn and/or other inflammatory stimuli. The skin disease or condition treated may be actinic keratosis (AK); skin cancer; a pre-cancerous growth; a skin disease or condition resulting from pre-emptive or post testing for an allergy; sunburn; a skin disease or condition resulting from a radiotherapy treatment; a skin disease or condition resulting from a tattoo; urticaria; eczema and other forms of dermatitis; a burns. The mucosal disease or treatment may be a

cough; sinusitis; and/or post-chemotherapy bladder pain.

The composition may also be used to prepare skin for one or more procedure such as, PDT or a tattoo.

The menthol may be present in a concentration of 0.1 to 5 %. The menthol concentration may be 0.25 to 2.0 %. The menthol concentration may be 0.4 to 0.6 %. The menthol concentration may be 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0 %. In one embodiment the menthol concentration is 0.5%.

The ginseng may be Panax ginseng (Asian ginseng) or *Panax quinquefolius* (American ginseng). The Panax ginseng may be fresh ginseng, white ginseng, red ginseng or sun ginseng. In one embodiment the ginseng is Panax ginseng.

The ginseng may be present as an extract. The ginseng extract may be a commercially available extract.

The ginseng extract may be present in a concentration of 1 to 10%. The ginseng extract may be present in a concentration of 2.5 to 7.5 %. The ginseng extract may be present in a concentration of 4 to 6 %. The concentration may be 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9,

9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9 or 10.0 %. In one embodiment the concentration of the ginseng extract is 5.0 %.

The composition may comprise one or more emollient. Suitable emollients include paraffin and aloe vera.

The composition may also comprise one or more pain reliever.

The one or more pain reliever may include an agent that blocks noxious signalling from one or more receptor.

The noxious signaling blocked may be noxious signaling from the transient receptor potential vanilloid receptor 1. The blocking may be specific to the transient receptor potential vanilloid receptor 1.

The menthol blocks the transient receptor potential melastatin 8 (TRPM8) receptor. The menthol may specifically block the TRPM8 receptor.

The composition may further comprise an agent which helps seal disrupted inter-epithelial surfaces. The agent may be a ceremide compound such as lanoline, an oil base such as avocado oil or in paraffin.

The composition may further comprise a topical anaesthetic.

The composition may also comprise one or more anti-inflammatory, one or more anti-histamine and or one or more anti-prostaglandin.

The anti-inflammatory may be an oral anti-inflammatory medication such as, fexofenidine, ceterizine or a non-steroidal anti-inflammatory drug (NSAID) such as, aspirin.

The above anti-inflammatory may also have some action on the neurokinin (NK1) and acetylcholine (ACH) receptors.

The anti-prostaglandin may be a non-steroidal anti-inflammatory such

as aspirin, flunixin meglumine, dipyrone and phenylbutazone.

The composition may also comprise one or more medicament for blocking a prostanoid such as, a NSAID such as, aspirin.

The ginseng may reduce a leukotriene. The leukotriene reduced may be leukotriene B4.

The composition may further comprise a sunscreen.

The sunscreen advantageously reduces ongoing activation of the one or more photosensitizer.

The menthol and ginseng comprising composition may be used to treat any type of pain. The pain may be pain associated with light therapy, laser therapy, radiotherapy, burns, inflammation and/or mucosal inflammation.

The present invention also provides methods and compositions for treating and/or prevention of a skin disease or skin condition. While the methods and compositions are explained with reference to photodynamic therapy (PDT), they are not constrained thereto.

A second composition for treating and/or prevention of a skin or mucosal disease or condition may comprise one or more alpha hydoxy acid (AHA).

An AHA is a compound that comprises a carboxylic acid substituted with a hydroxyl group on the adjacent carbon. The one or more AHA may be selected from the group consisting of glycolic acid, lactic acid, citric acid, malic acid, tartaric acid and mandelic acid. Preferably, the one or more AHA has a small molecular size so that it is able to penetrate the top layer of the

skin.

The one or more AHA in the composition may be at a concentration in the range of 2 to 20%. The one or more AHA in the composition may be in a concentration range of 5 to 15 %. The one or more AHA in the composition may be in a concentration range of 8 to 12 %. The concentration may be 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20%. In one embodiment the one or more AHA in the composition is in a concentration of 10 %.

If the area of skin being treated is on the face or other sensitive area the concentration of the one or more AHA may be in the range of 2 to 10 %. The concentration may be in the range of 4 to 6 %. In one embodiment the concentration is 5%.

FIG. 1A shows one embodiment of a method 100 according to the invention. Method 100 includes a step 102 of treating an area of skin with the composition comprising one or more alpha hydroxy acid according to the invention.

Method 100 also includes step 104 of applying one or more photosensitizer to the area of skin.

Then in step 106 the area of skin is exposed to light to thereby prevent and/or treat the skin disease and or condition.

The treatment of the area of skin with a composition comprising one or more alpha hydroxyl amino acid may be for any suitable period. Suitably, the period is sufficient for the integrity of the skin to be improved.

The treatment may be for 1 day to 4 weeks. The treatment may be 1

day, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, 3 weeks or 4 weeks. Preferably the treatment is for 2 to 4 weeks.

The treatment may be between one and five times a day or as needed.

The treatment of the area of skin with a composition comprising one or more hydroxyl amino acid is a chemical treatment. The treatment may also include a physical treatment such as, exfoliation.

The treatment may also include washing the area of skin. The washing may be with a ceramide.

The present inventors have discovered that one of the significant advantages of the present invention is that exposure to the one or more AHA normalizes and stabilizes the skin, improving the skin integrity and the integrity of the lipid intracellular barrier. The normalized and stabilized skin is more receptive to PDT and thereby the efficacy of the PDT therapy is increased.

Although not wanting to be bound by any theory, by improving the integrity of the area of skin the nerves are not as exposed which means less photosensitizer may be used because application is to a relatively smoother surface. Consequently, there is also less light scatter, better light penetration, less pain, better tolerance and higher compliance with the method of the invention.

The one or more photosensitizer applied may be aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), silicon phthalocyanine (Pc 4), m-

tetrahydroxyphenylchlorin (mTHPC), mono-L-aspartyl chlorin e6 (NPe6), Photofrin, Visudyne and/or LS11. Preferably the one or more photosensitizer is ALA.

The ALA may be stabilized.

The novel stabilized form of ALA provided by the present invention has an improved shelf life of three months and thereby has many advantages over single use bottles such as, ability to evenly distribute the ALA on the area of skin, ability to use any remainder on subsequent subject and decreased cost.

The ability to evenly distribute the ALA on the skin also means that lower intensity light may be used in PDT and also that decreased pain is encountered. Further advantages such as better tolerance and increased patient compliance flow from these significant advantages of the invention.

The exposure to light may comprise exposure to two or more discrete wavelengths of light. Preferably the two or more wavelengths comprise blue light and red light. Preferably the exposure is to blue light and then to red light.

The exposure to blue light may be for between 2 and 20 minutes. The exposure may be for 5 to 15 minutes. The exposure may be for between 8 and 12 minutes. The exposure to blue light may be for 2, 3, 4, 5, 6, 7, 8 , 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 minutes. In one embodiment the exposure to blue light is for 10 minutes.

The exposure to red light may be for between 5 and 30 minutes. The exposure to red light may be for between 15 and 25 minutes. The exposure

to red light may be for between 18 and 22 minutes. The exposure to red light may be for 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 minutes. In one embodiment the exposure to red light is for 20 minutes.

By discrete wavelength is meant exposure to light of only or substantially only of a wavelength or a range of wavelengths. For example, exposure to sunlight or white light is not exposure to discrete light and is instead exposure to a wide spectrum of light.

The blue light may have a wavelength between 450 and 495 nm. The wavelength may be between 460 and 490 nm. The wavelength may be between 460 and 480 nm. The wavelength may be 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494 or 495 nm. In one embodiment the wavelength is 470 nm.

The red light may have a wavelength between 620 and 750 nm. The wavelength may be between 630 and 700 nm. The wavelength may be between 635 and 645 nm. The wavelength may be 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 675, 680, 685, 690, 695, 700, 705, 710, 715, 720, 725, 730, 735, 740, 745 or 750 nm. In one embodiment the wavelength is 640nm.

The exposure to light may activate the photosensitizer. Accordingly, the light wavelength and/or exposure time may be selected to activate the photosensitizer. A person of skill in the art may alter the light wavelength and/or exposure time to suit a particular photosensitizer.

The exposure to light may also include exposure to laser light and or intense pulsed light (IPL).

The method 100 may also be combined with one or more physical treatment. The physical treatment may be a physical intervention on the area of skin such as, a surgical method, an excision or cryotherapy.

While not wanting to be bound by any theory, the present inventors hypothesize that there is no medical or pharmacological interaction between the AHA's and the one or more photosensitizer. However, their combined use has synergistically led to advantages such as less pain, better tolerance and increased compliance.

FIG. 1B shows another embodiment of the method 100 of the invention comprising the step 108 of post-treating the area of skin.

The post-treatment may be treatment with the composition comprising menthol and ginseng according to the invention. The composition may also comprise any of the further components of the composition identified herein.

The post-treatment may further include avoidance of direct and indirect sunlight.

Advantageously, the post-treatment blocks sensory nociceptors, re-establishes epithelial integrity by the emollient properties as well as by the use of an agent to help seal disrupted inter-epithelial surfaces and thereby

reduces pain and reduces transepidermal water loss.

The post-treatment composition may be combined with one or more co-therapeutic. The one or more co-therapeutic may comprise imiquimod and/or 5-fluorouracil.

Imiquimod or Aldara™ is 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-4-amine and has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Imiquimod may be applied topically to the area of skin after and/or as part of post-treatment.

5-fluorouracil may be applied as Efudix™. 5-fluorouracil may be applied topically to the area of skin after and/or as part of post-treatment.

The invention also provides a second method 200 for preventing and/or treating a skin disease or condition, shown in FIG. 1C, which includes a step 202 of treating an area of skin with the composition comprising menthol and ginseng described above. The composition may also comprise any of the further components of the composition identified herein.

Method 200 also includes step 204 in which one or more photosensitizer is also be applied to the area of skin.

Then in step 206 the area of skin is exposed to light to thereby prevent and/or treat the skin disease and or condition.

Step 202 may be conducted prior to exposure to light, during exposure to light and/or after exposure to light.

FIG. 1D shows an additional step 208 in which the area of skin is treated with the composition comprising one or more AHA described above. Preferably step 208 is conducted prior to step 206 in which the area of skin is

exposed to light.

As with method 100, the one or more photosensitizer applied in method 200 may be aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), silicon phthalocyanine (Pc 4), m-tetrahydroxyphenylchlorin (mTHPC), mono-L-aspartyl chlorin e6 (NPe6), Photofrin, Visudyne and/or LS11. Preferably the one or more photosensitizer is ALA.

The ALA may be stabilized.

The exposure to light in method 200 may be as described with reference to method 100.

The method 200 may also be combined with one or more physical treatment. The physical treatment may be a physical intervention on the area of skin such as, a surgical method, an excision or cryotherapy.

Method 200 may also include avoidance of direct and indirect sunlight post-treatment.

The compounds referred to herein may be applied as a pharmaceutically acceptable salt thereof.

The term "pharmaceutically acceptable salts" as used herein refers to salts which are toxicologically safe for systemic administration. The pharmaceutically acceptable salts may be selected from the group including alkali and alkali earth, ammonium, aluminium, iron, amine, glucosamine, chloride, sulphate, sulphonate, bisulphate, nitrate, citrate, tartrate, bitarate, phosphate, carbonate, bicarbonate, malate, maleate, napsylate, fumarate, succinate, acetate, benzoate, terephthalate, pamoate, pectinate and s-methyl methionine salts piperazine and the like.

The compositions of the invention may comprise an effective amount of one or more relevant compounds, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically acceptable carrier, diluent and/or excipient.

The excipient may be present in a concentration of 0.1 to 5.0 %. The excipient may be present in a concentration of 1.0 to 3.0 %. The excipient may be present in a concentration of 1.5 to 2.5 %. The excipient may be present in a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9 or 5.0 %. In one embodiment the excipient is present in an amount of 2.0 %.

In one embodiment the excipient is polysorbate 20.

The compositions of the invention may comprise an effective amount of a solvent. In one embodiment the solvent is water.

Dosage form and rates for pharmaceutical use and compositions are readily determinable by a person of skill in the art.

Dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches, creams, gels and the like. These dosage forms may also include injecting or implanting devices designed specifically for, or modified to, controlled release of the pharmaceutical composition. Controlled release of the therapeutic agent may be effected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polyactic and polyglycolic acids and certain cellulose derivates such

as hydroxypropylmethyl cellulose. In addition, the controlled release may be affected by using other polymer matrices, liposomes and/or microspheres.

Pharmaceutically acceptable carriers and acceptable carriers for systemic administration may also be incorporated into the compositions of this invention.

Suitably, the pharmaceutical composition comprises a pharmaceutically-acceptable excipient or an acceptable excipient. By "pharmaceutically-acceptable excipient" is meant a solid or liquid filler, diluent or encapsulating substance that may be safely used. Depending upon the particular route of administration, a variety of carriers, well known in the art may be used. These carriers or excipients may be selected from a group including sugars, starches, cellulose and its derivates, malt, gelatine, talc, calcium sulphate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

Any suitable route of administration may be employed for providing a human or non-human patient with the pharmaceutical composition of the invention. For example, oral, rectal, parenteral, sublingual, buccal, intravenous, intraarticular, intra-muscular, intra-dermal, subcutaneous, inhalational, intraocular, intraperitoneal, intracerebroventricular, transdermal, topical and the like may be employed. In one embodiment the pharmaceutical composition is applied topically. When treating a mucosal disease or condition the composition of the invention may be atomized, nebulised or instilled.

Pharmaceutical compositions of the present invention suitable for administration may be presented in discrete units such as vials, capsules, sachets or tablets each containing a predetermined amount of one or more pharmaceutically active compounds of the invention, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil emulsion or as a solution or suspension in a cream or gel. Such compositions may be prepared by any of method of pharmacy but all methods include the step of bringing into association one or more pharmaceutically active compounds of the invention with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the agents of the invention with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product in to the desired presentation.

The active compounds of the compositions of this invention may be present in an amount sufficient to prevent, inhibit or ameliorate a disease or condition. Suitable dosages of the compounds and the pharmaceutical compositions containing such may be readily determined by those skilled in the art.

So that the invention may be readily understood and put into practical effect, the following non-limiting Examples are provided

EXAMPLES

EXAMPLE 1

A composition comprising 2.00% polysorbate 20, 0.50 % liquid

menthol 0.50, 5.00 % panax ginseng (hydroglyceric) extract was prepared in water to 100%.

EXAMPLE 2

FIGS. 2A-2C shows a subject at initial consult with obvious AKs and skin abnormalities. FIGS. 2D-2F show the subject 10 weeks after receiving two PDT treatments according to the invention and show much improved skin clarity, stability and normality.

The composition of Example 1 was applied to the skin of the treatment area ten (10) minutes prior to treatment with photodynamic therapy. Care was taken to avoid mucosal membrane contact.

If the patient experienced pain during illumination with the PDT lights, the composition of example 1 was applied again as required.

Likewise, after exposure to the PDT lights if pain continued the composition of example 1 was again applied as required.

FIG. 2G and 2H shows punch biopsy results for residual suspicious lesions for the subject. The subject had squamous-cell carcinoma (SCC) *in situ* below the right eye as well as above the left eye, well differentiated SCC below the left eye and a superficially invasive well differentiated SCC near the left ear.

EXAMPLE 3

During and following PDT treatment the composition of Example 1 was applied to the area of skin treated. Acute pain was reduced by

approximately 90% during PDT treatment and reduced by approximately 80% when used 1 and 2 days post-PDT treatment.

The present invention has improved efficiency and reduced pain as compared to other methods and compositions.

The present invention advantageously reduces cancers and related pre-cancerous lesions within the field or area around prior cancers or lesions.

The present invention provides a holistic process of skin stabilization and normalisation followed by a precise, two-wavelength PDT, which may be followed by post-treatment modalities. This novel approach is especially promising for treating the 'field' or broad area impacted by skin cancers, with the expectation of reducing or eliminating future recurrence.

Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. It will therefore be appreciated by those of skill in the art that, in light of the instant disclosure, various modifications and changes can be made in the particular embodiments exemplified without departing from the scope of the present invention.

All computer programs, algorithms, industrial, patent and scientific literature referred to herein is incorporated herein by reference.

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CLAIMS

1. A composition for treating pain and/or inflammation comprising menthol, ginseng and an emollient.

2. The composition according to claim 1 comprising menthol at a concentration of 0.1 to 5 %.

3. The composition according to claim 1 comprising menthol at a concentration of 0.5%.

4. The composition according to claim 1 wherein the ginseng comprises Panax ginseng (Asian ginseng) and/or *Panax quinquefolius* (American ginseng).

5. The composition according to claim 1 according to claim 1 wherein the ginseng is Panax ginseng.

6. The composition according to claim 5 wherein the Panax ginseng is selected from the group consisting of fresh ginseng, white ginseng, red ginseng or sun ginseng.

7. The composition according to claim 1 wherein the ginseng is an extract.

8. The composition according to claim 1 wherein the ginseng is at a concentration of 1 to 10%.

9. The composition according to claim 1 wherein the ginseng is at a concentration of 5 %.

10. The composition according to claim 1 wherein the emollient is paraffin and/or aloe vera.

11. A method for treating pain and/or inflammation including the step of applying the composition comprising menthol, ginseng and an emollient to thereby treat the pain and/or inflammation.

12. Use of a composition comprising menthol, ginseng and an emollient in the manufacture of a medicament for treatment of pain and/or inflammation.

13. The method according to claim 11 or the use of claim 12 wherein the pain and/or inflammation treated includes acute inflammation and/or late phase response to a burn and/or other inflammatory stimuli.

14. The method according to claim 11 or the use of claim 12 wherein the pain and/or inflammation treated comprises pain and/or inflammation associated with a photodermatological method.

15. A composition for treating a skin disease and/or a skin condition comprising one or more stabilised alpha hydroxyl acid.

16. The composition according to claim 15 wherein the one or more alpha hydroxyl acid is selected from the group consisting of glycolic acid, lactic acid, citric acid, malic acid, tartaric acid and mandelic acid.

17. The composition according to claim 15 wherein the one or more alpha hydroxyl acid is at a concentration in the range of 2 to 20%.

18. A method for treating a skin disease or a skin condition including the step of applying a composition comprising one or more alpha hydroxy acid to thereby treat the skin disease or skin condition.

19. Use of a composition comprising one or more alpha hydroxy acid in the manufacture of a medicament for treatment of a skin disease or a skin condition.

20. A method for preventing and/or treating a skin disease or skin condition including the steps of:

treating an area of skin with a composition comprising menthol and ginseng;

applying one or more photosensitizer to the area of skin; and

exposing the area of skin to light to thereby prevent and/or treat the skin disease and or condition.

21. The method of claim 20 further including the step of treating the area of skin with a composition comprising one or more alpha hydroxy acid.

22. A method for preventing and/or treating a skin disease or skin condition including the steps of:

treating an area of skin with a composition comprising one or more alpha hydroxyl acid;

applying one or more photosensitizer to the area of skin; and

exposing the area of skin to light to thereby prevent and/or treat the skin disease and or condition.

23. The method of claim 22 further including a step of treating the area of skin with a composition comprising menthol, ginseng and an emollient.

24. The method of claim 20 or claim 22 wherein the light comprises two or more wavelengths.

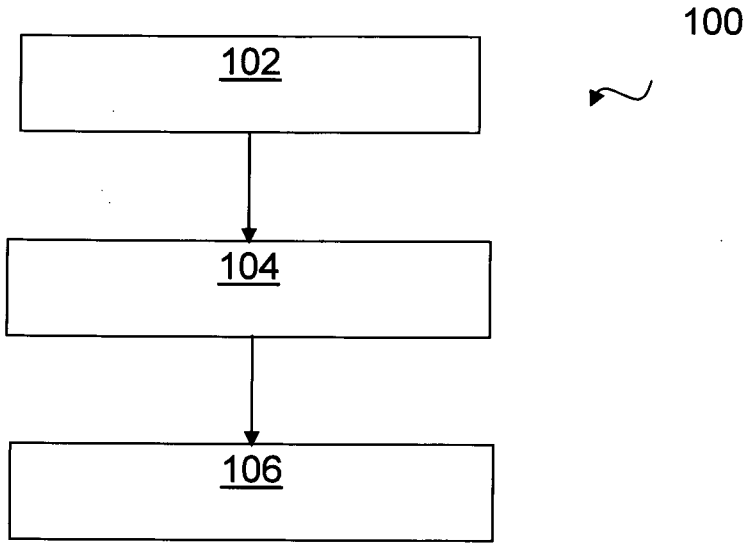

FIG. 1A

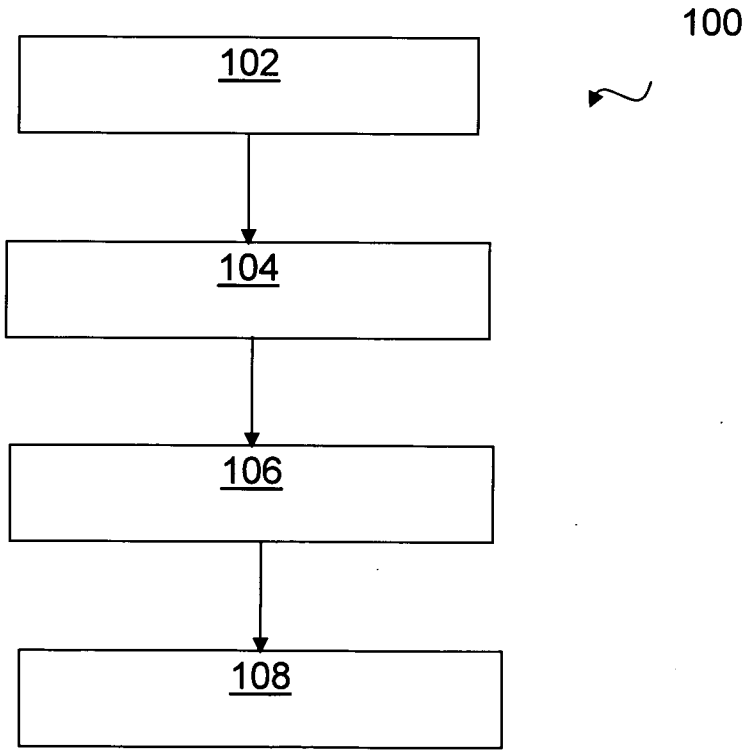

FIG. 1B

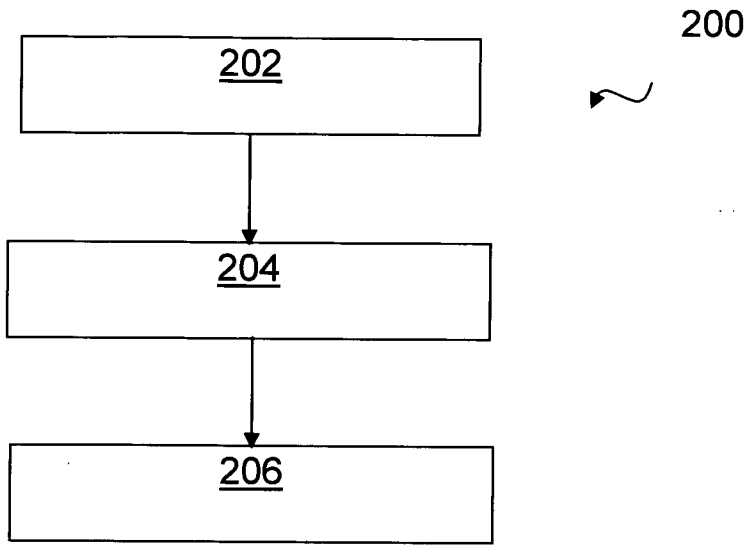

FIG. 1C

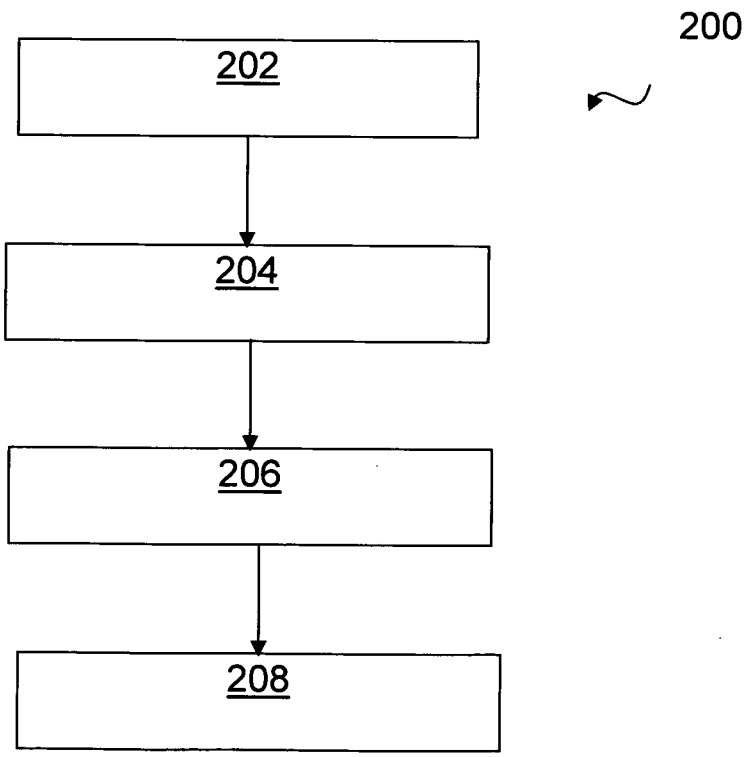

FIG. 1D

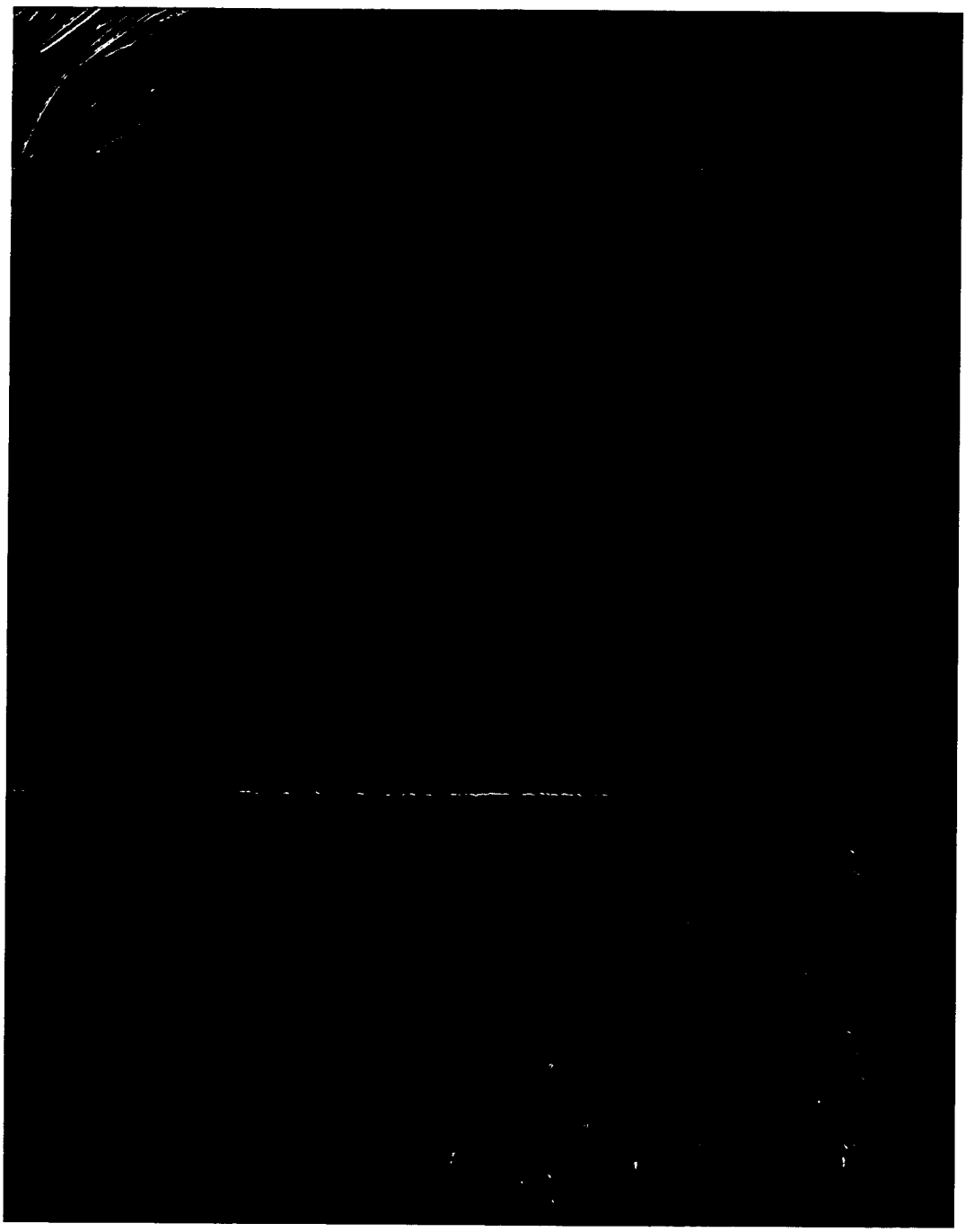

FIG. 2A

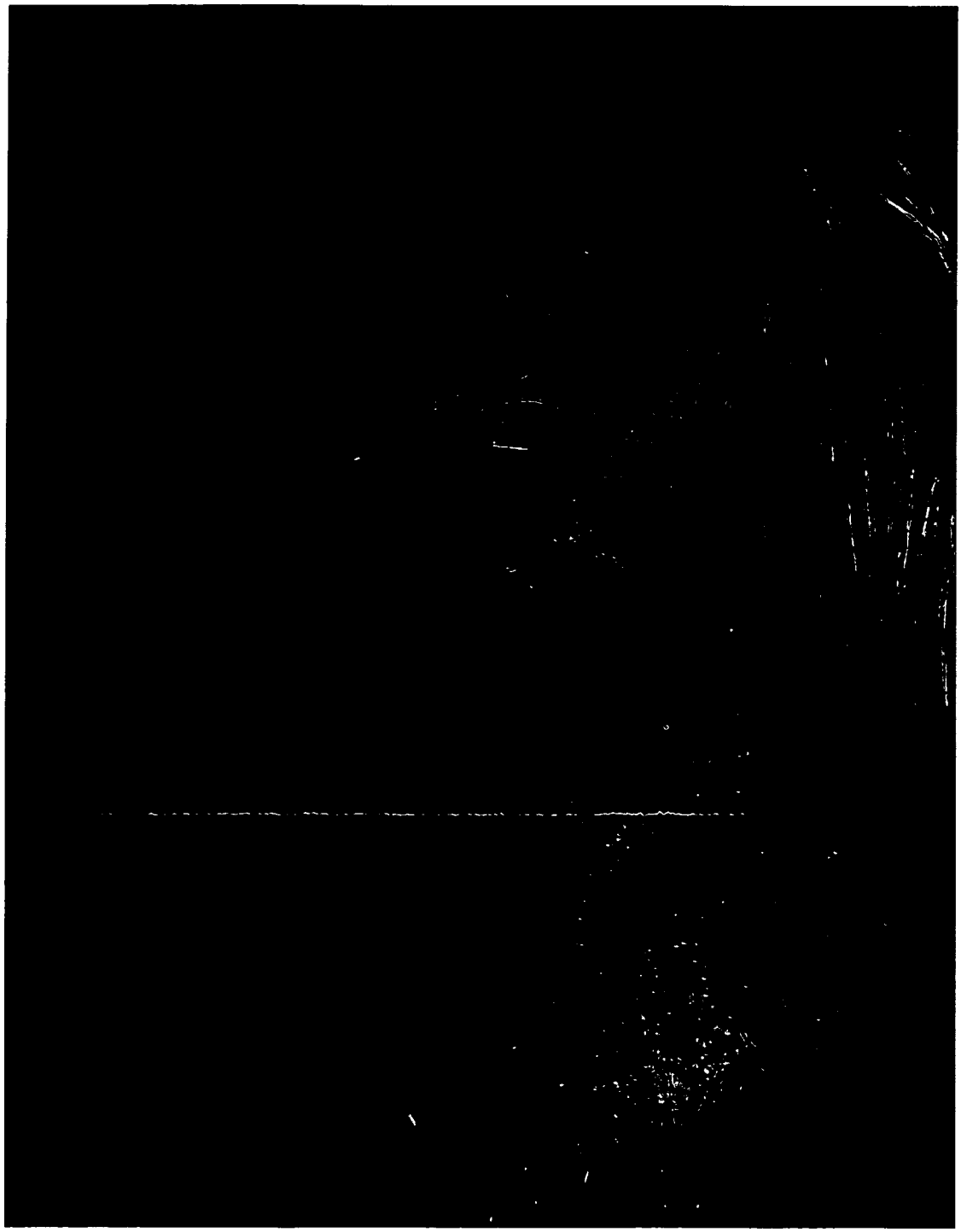

FIG. 2B

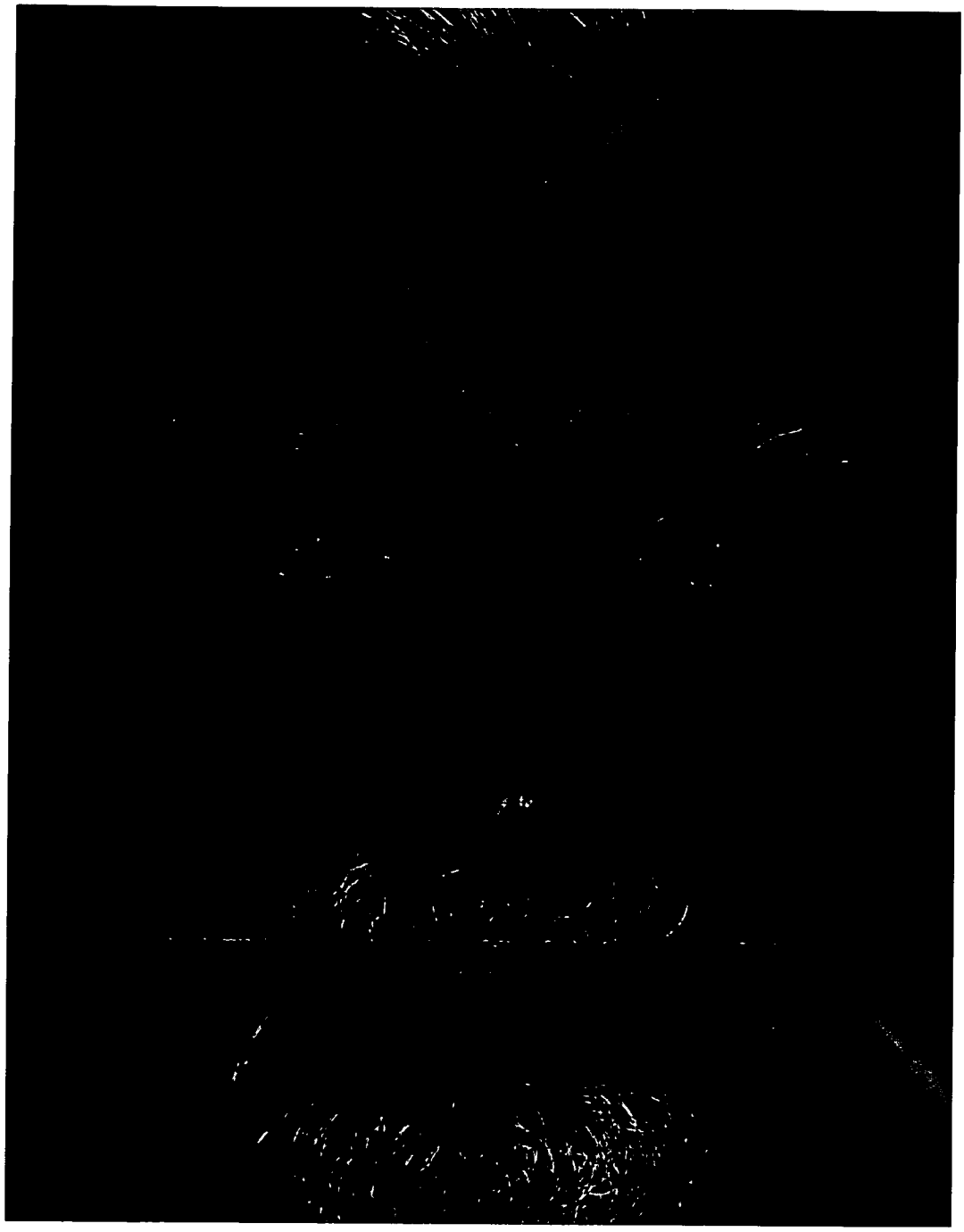

FIG. 2C

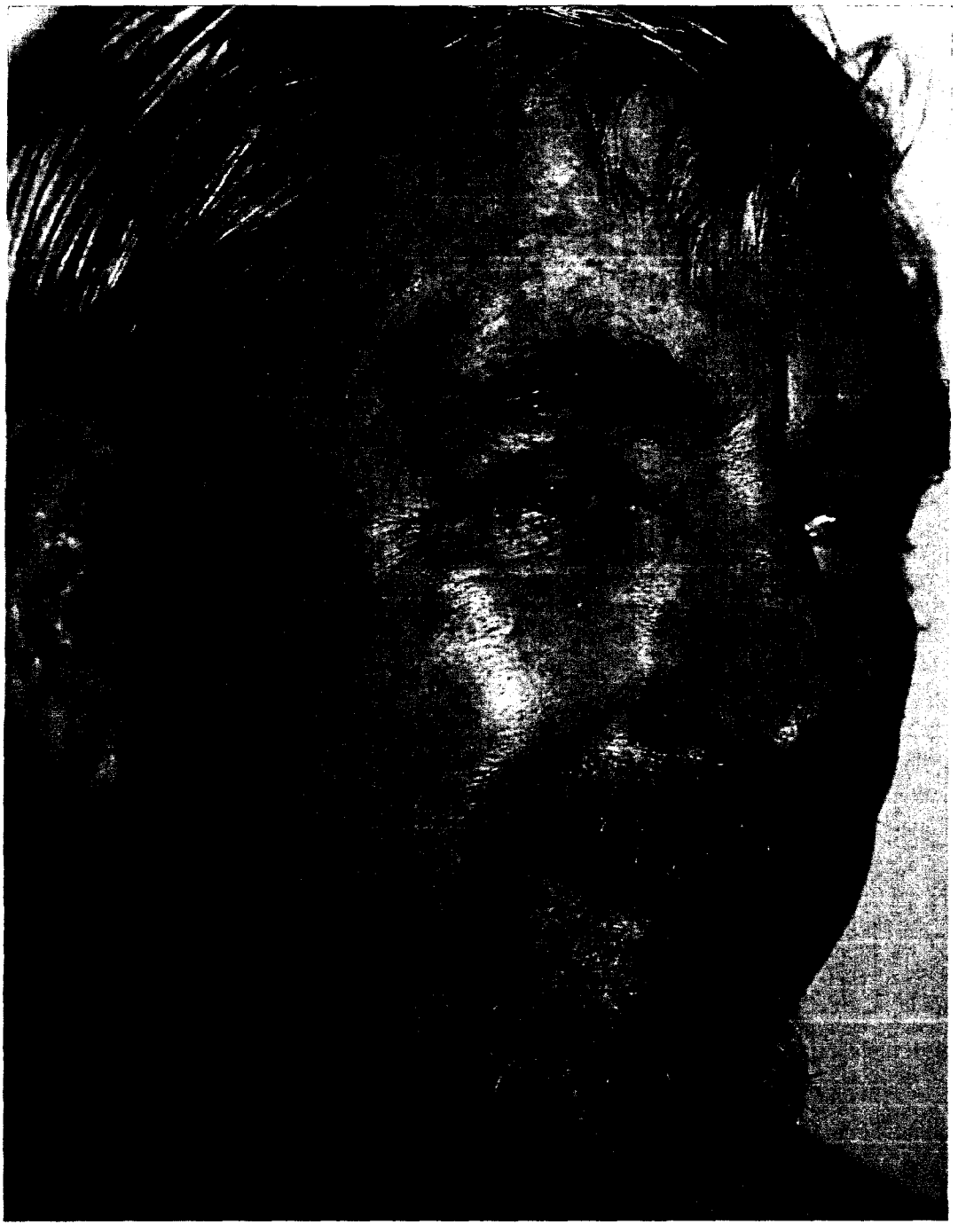

FIG. 2D

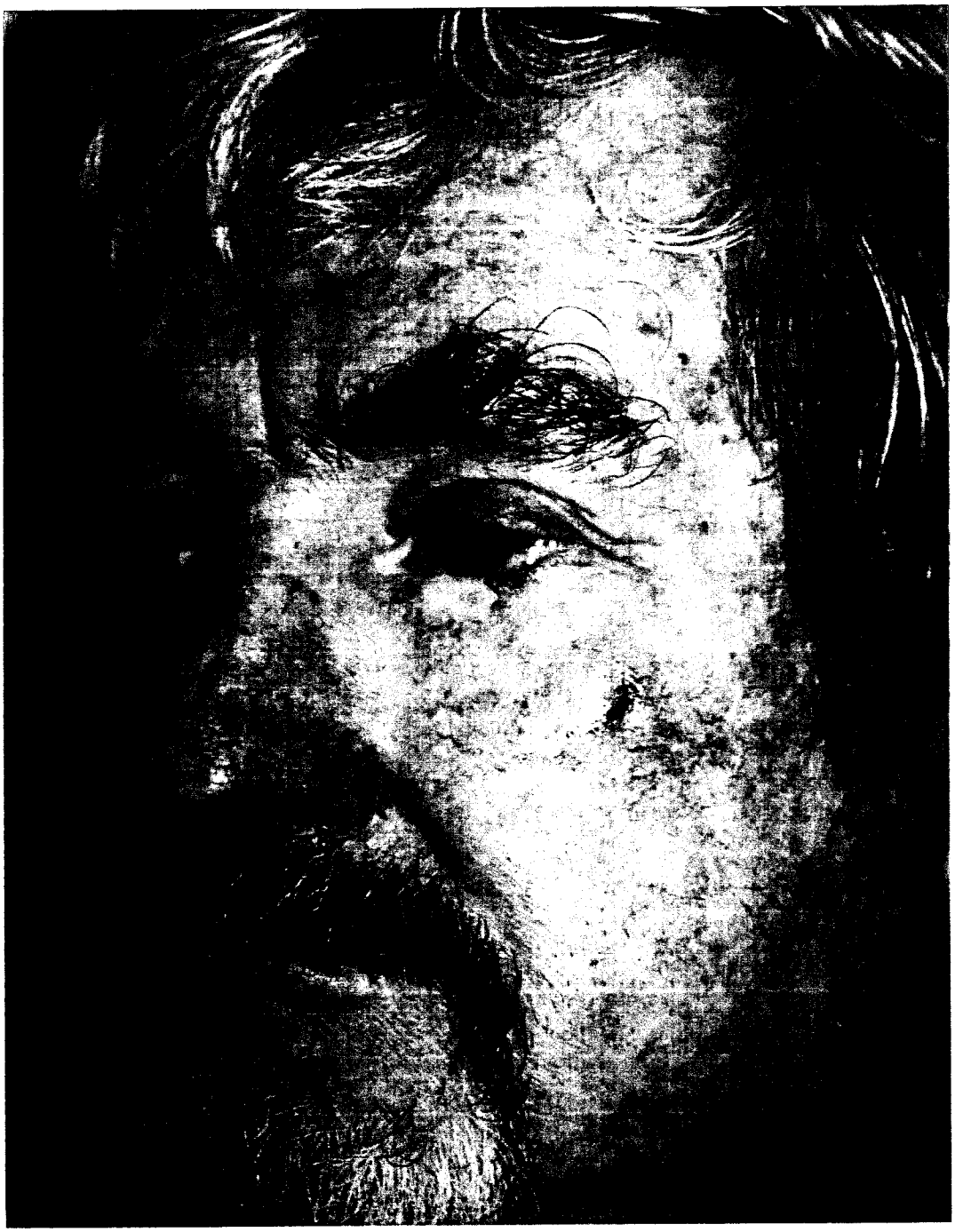

FIG. 2E

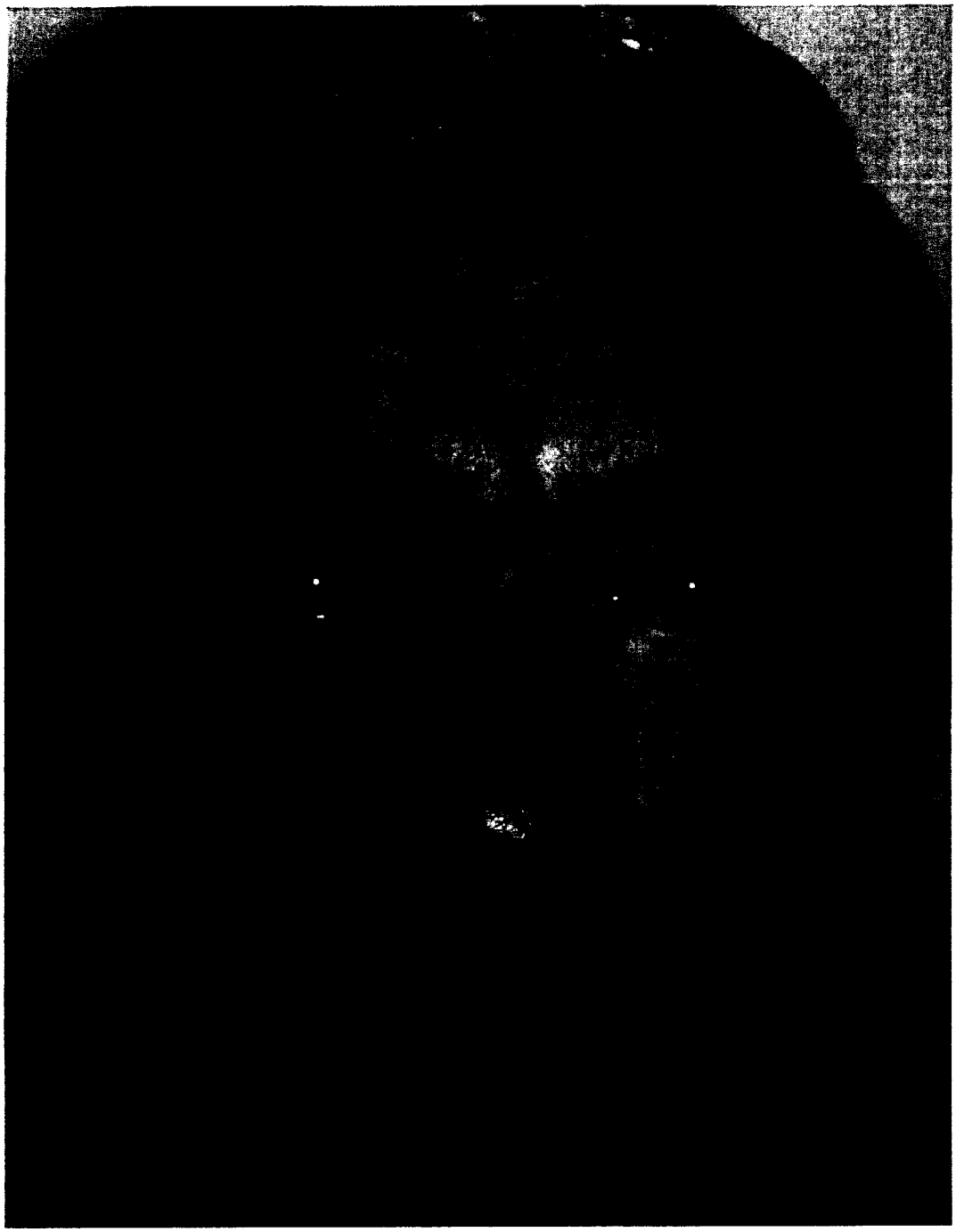

FIG. 2F

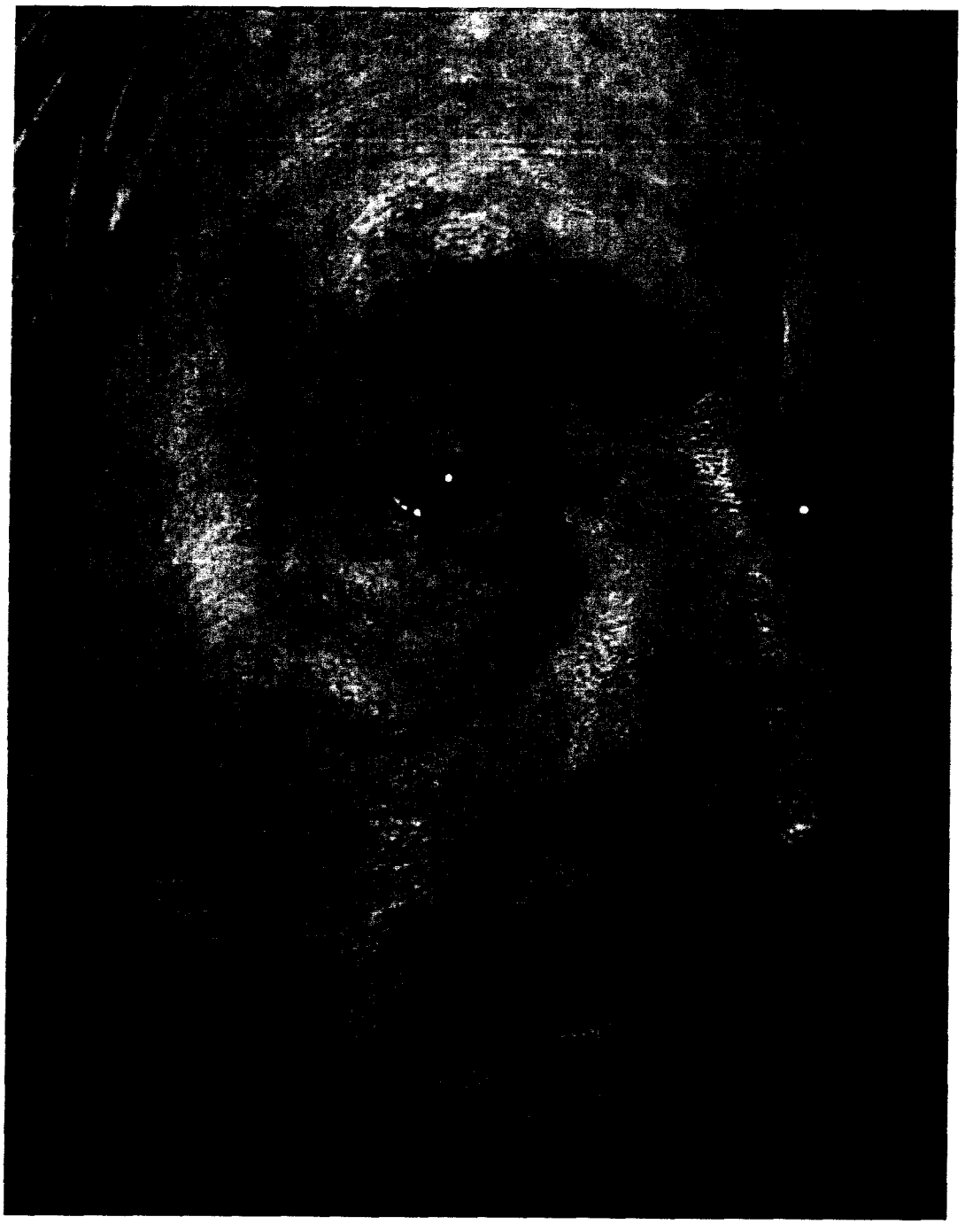

FIG. 2G

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000539

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61K 36/258 (2006.01) *A61P 43/00* (2006.01)

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)

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)
Epodoc, WPI, Medline & XPTK keywords; ginseng+, panax+, menthol+, inflamm+, and like terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/010958 A2 (SHAKLEE CORPORATION) 5 February 2004 See abstract; examples; claims	1, 4, 5, 7, 9
X	US 5124320 A (IVY et al.) 23 June 1992 See abstract; column 1, lines 25-30 & 38-43 and 53-57; column 2, lines 44-47; claims	1-4, 9-14
X	JP 2006-335680 A (GERO KOSHA KK) 14 December 2006 See abstract; [0015]; [0018]-[0020]; [0027]-[0029]; claims	1, 7-10
X	CN 1202364 A (ATTACHED HOSPITAL NO 1 HUNAN COLLEGE) 23 December 1998 See abstract; claims	1, 4-9, 11-14

[X] Further documents are listed in the continuation of Box C [X] 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2010	25 AUG 2010

Name and mailing address of the ISA/AU

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000539

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box I

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-14

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/000539

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6399082 B1 (GANEMO) 4 June 2002 See whole document	
A	US 5760079 A (SHAFFER et al.) 2 June 1998 See whole document	

Supplemental Box I
(To be used when the space in any of Boxes I to IV is not sufficient)

Continuation of Box No. III

This International Application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept.

In assessing whether there is more than one invention claimed, I have given consideration to those features which can be considered to potentially distinguish the claimed combination of features from the prior art. Where different claims have different distinguishing features they define different inventions.

This International Searching Authority has found that there are different inventions as follows:

- Invention 1: Claims 1-14 fully, are directed towards formulations of menthol, ginseng and an emollient, and the use of such formulations in treating pain and/or inflammation.

  It is considered that formulations of menthol, ginseng and an emollient, and use of such formulations in treating pain and/or inflammation comprises a first distinguishing feature.

- Invention 2: Claims 15-19 fully, are directed towards formulations and use of the formulations of one or more alpha hydroxy acid in treating skin diseases and/or skin conditions.

  It is considered that formulations and the use of formulations of one or more alpha hydroxy acid in treating skin diseases and/or skin conditions comprises a second distinguishing feature.

- Invention 3: Claims 20 and 21 fully, and 24 partially, are directed towards a method for preventing and/or treating a skin disease or skin condition comprising administering a composition comprising menthol and ginseng and applying one or more photosensitizer to the area of skin; and exposing the area of skin to light.

  It is considered that a method for preventing and/or treating a skin disease or skin condition by administering a composition comprising menthol and ginseng, and applying one or more photosensitizer; and exposing the area of skin to light comprises a third distinguishing feature.

- Invention 4: Claims 22 and 23 fully, and claim 24 partially, are directed towards a method for preventing and/or treating a skin disease or skin condition by administering a composition comprising one or more alpha hydroxy acid; applying one or more photosensitizer to the area of skin; and exposing the area of skin to light.

  It is considered that a method for preventing and/or treating a skin disease or skin condition by administering a composition comprising one or more alpha hydroxy acid; applying one or more photosensitizer to the area of skin; and exposing the area of skin to light comprises a fourth distinguishing feature.

  PCT Rule 13.2, first sentence, states that unity of invention is only fulfilled when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. PCT Rule 13.2, second sentence, defines a special technical feature as a feature which makes a contribution over the prior art.

  The only common feature to inventions 2 and 4 is the method of treating skin diseases and/or skin conditions by administering one or more alpha hydroxy acid. However this concept is not novel in light of:

  D5: US 6399082 B1 (GANEMO) 4 June 2002
  D6: US 5760079 A (SHAFFER et al.) 2 June 1998

Continued in Supplemental Box II

Supplemental Box II
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Supplemental Box I

D5 discloses the use of compositions comprising an alpha hydroxy acid for the topical treatment of hyperkeratotic skin diseases (abstract).

D6 discloses methods of treating and/or preventing striae distensae lesions by topically applying compositions containing alpha hydroxy acid (abstract).

This means that the common feature to inventions 2 and 4 cannot be a special technical feature within the meaning of PCT Rule 13.2, second sentence, since it makes no contribution over the prior art.

Each of the abovementioned groups of claims has a different distinguishing feature and they do not share any feature which could satisfy the requirement for being a special technical feature. Because there is no common special technical feature it follows that there is no technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention *a posteriori.*

As the search and examination for the additional inventions will each require more than negligible additional search and examination effort over that for the first invention and each other, three additional search fees are warranted.

For the fee already paid, the ISA will search the first claimed invention defined by claims 1-14 fully.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2010/000539

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2004010958	AU	2003257143	US	2004110650	US	7025955
US	5124320	CA	2025078	EP	0443007	HK	48897
		US	5013726	WO	9104010		
JP	2006335680	NONE					
CN	1202364	NONE					
US	6399082	AU	19659/99	BG	104470	BR	9815016
		CA	2310049	CN	1280495	CZ	20001920
		EP	1032378	HK	1034194	HU	0100066
		IS	5505	NO	20002649	NZ	504458
		PL	340679	SK	7432000	WO	9926617
US	5760079	AU	26453/95	CA	2190377	EP	0760659
		MX	9605753	US	5444091	WO	9531980

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX