Abstract:
The present invention relates to the use of ginsenosides and a plant extract containing ginsenosides in a cosmetic or pharmaceutical composition or in a food supplement for the protection of the skin against deleterious effects of stress or irradiation e.g. sunlight or UV irradiation.
Use of Ginsenosides and Extracts Containing Them

The present invention relates to the use of ginsenosides and a plant extract containing ginsenosides in a cosmecically or pharmaceutical composition or in a food supplement for the protection of the skin against deleterious effects of stress or irradiation such as sunlight or UV irradiation.

The Panax plant family comprises numerous species such as Panax ginseng (C.A.Meyer), Panax quinquefolium, and Panax notoginseng which are cultivated and used industrially in food supplements, pharmaceuticals and cosmetics. They contain saponins as active substances which are called ginsenosides. Ginsenosides of each species are basically the same, but are contained in different proportions in each species.

Panax notoginseng (also called San Qi) is a straight herbaceous perennial plant which grows e.g. in the southwest of China. Traditionally people use the roots of Panax notoginseng not only as a tonic but also for the treatment of many symptoms and diseases such as trauma, inflammation, hepatitis, heart and vascular diseases as well as aging. Up to now more than 30 ginsenosides could be isolated from the roots of Panax notogingseng. The major ginsenosides are ginsenoside RgI and ginsenoside RbI followed by ginsenosides Rd, Re, Rg2 and notoginsenoside Rl. Many scientific works have confirmed the pharmacological properties and biological activities of Panax notoginseng such as ditropism regulating effects to organic function (Y.M. Luo et al., Acta Pharmacologica Sinica, 1993, 14(5), 401-404), effects on the central nervous system (Y. Ying et al., Acta Pharmacutica Sinica, 1994, 29(4), 241-245), cancer prevention (T. Konoshima et al., Chemical and Pharmaceutical Bulletin, 1992, 40, 531-533; L. Xu et al., Journal of WCUMS, 1991, 22(2), 124-127) and antiviral activity (J. Li et al., Journal of Norman Bethune University of Medical Sciences, 1992, 18(1), 24-26).

In the cosmetic industry, Panax notoginseng and/or ginsenosides are used for various applications. Panax notoginseng extract is claimed for skin elasticity activation to improve wrinkles and prevent chronological and UV-induced aging (JP 2006-028 150).

Ginsenoside RbI or Rb-I like substances are described for stimulation of elastin synthesis (WO 99/07338), for treating hair (FR 9300899, US 5,663,160), for stimulating the regeneration of tissues after the wound (JP 2002-255826), for the reconstruction of tissues suffering from skin aging (WO 2002/072599), for treating wounds in the case of burns (JP 2004-077456). Ginsenoside RbI is also used in combination with Ginsenosides Rc and Rd (JP 2003-070496) to activate endonuclease for the repair of UV damaged DNA. Ginsenosides Rh2 and Rg3 are blended in a UV-blocking cosmetic composition due to their UV absorbing properties (KR 2004-0098177).
Langerhans cells are responsible for the immune protection of skin. When skin is exposed to UV light, Langerhans cells disappear from the epidermis and as a result it becomes less protected against infectious diseases and cancer (T. Schwarz, Photodermatol Photoimmunol Photomed 2002, 18, 141-145).

Heme oxygenase HO is an enzyme which catalyzes the ring opening of heme (a molecule found in cells) with the formation of carbon monoxide CO, biliverdin (which is rapidly transformed into the antioxidant bilirubin) and free iron (which leads to the induction of the iron-binding protein ferritin). Heme oxygenase has two forms: HO-2 which is the constitutive form mainly in neural tissues and HO-I which is the inducible form. They are considered to be cytoprotective enzymes due to the antioxidant, anti-inflammatory, anti-apoptotic and anti-proliferative effects (L.E. Otterbein et al., Trends Immunol. 2003, 24(8), 449-55). HO-I induction is considered to improve burn injury healing (Gan HT et al., Surgery., 2006, 141(3):385-93) and its induction by 20(S)-Protopanaxadiol is proved to decrease NO production for anti-inflammatory activity (Lee SH et al., Planta Med., 2005, 71(12), 1167-70). It has also been found that carbon monoxide generated by HO-I, which itself is generated by UV-A exposure, can protect Langerhans cells from photoimmunosuppression caused by UV-B irradiation (M. Allanson et al., J. Invest. Dermatol., 2005, 124(3), 644-650).

The present invention relates to ginsenosides and/or a plant extracts containing them for the protection of the skin against deleterious effects of stress or irradiation e.g. sunlight or UV irradiation.

The use of ginsenosides and the extracts containing them according to the invention are an appropriate and safe method for the protection of the skin.

According to the invention ginsenosides include but are not limited to the ginsenosides G-Ral, G-Ra2, G-Ra3, G-RbI, G-Rb2, G-Rb3, G-Rc, G-Rd, G-Re, G-Rf, G-RgI, G-Rg2, G-Rg3, G-Rhl, G-Rh2, G-Rsl, G-Rs2, G-Ro, MG-Rbl, MG-Rb2, MG-Rc, MG-Rd, Q-Rl, N-Rl, N-R4 and 20 Glc-Rf. Preference is given to ginsenoside G-RgI, G-Rbl, G-Rd, G-Re, G-Rg2 and N-Rl. Most preferably the ginsenoside is selected from the group consisting of ginsenoside G-RgI and G-Rbl.

All mentioned ginsenosides are known and can be isolated from the Panax plants by standard methods e.g. by extraction and chromatography.

According to the invention ginsenosides refers to a single ginsenoside as well as to a mixture of different ginsenosides. Preference is given to a mixture of ginsenosides comprising ginsenoside G-
Rgl and G-RbI, more preferably a mixture of ginsenoside G-RgI, G-RbI, G-Rd, G-Re, G-Rg2 and N-Rl.

Plant extracts containing ginsenosides according to the invention are extracts of plants of the Panax family which include but are not limited to Panax ginseng (C.A.Meyer), Panax quinquefolium, and Panax notoginseng (San Qi). Preference is given to Panax notoginseng (San Qi).

The extraction can be performed on all parts of the plant. Preferably the roots or rhizomes are extracted.

The extraction can be done by standard extraction methods. Preferably roots or rhizomes are extracted with a polar solvent applicable for extraction optionally by several times. The crude extract can be purified by chromatography. Optionally the fractions can be dried by spray-drying.

An extract according to the invention is normally a dry extract. Nevertheless the extract can also be used as solution, i.e. that the final drying step of the described extraction process is omitted and the product can optionally be encapsulated, e.g. in a gelatine capsule.

The polar solvent used for extraction is preferably alcohol or a mixture of water and alcohol wherein the alcohol is preferably ethanol.

Preference is given to a dry plant extract containing ginsenosides in an amount between 0.1 and 100%, preferably between 10 and 100%, preferably above 80%.

The extract according to the invention preferably contains G-RbI in an amount of from 10 to 60%, G-RgI in an amount of from 10 to 60%, G-Rd in an amount of from 0 to 15%, N-Rl in an amount of from 0 to 15 % and/or G-Re in an amount of from 0 to 10% by weight of the total extract.

Ginsenosides can be isolated and/or purified from the extract containing it by standard isolation methods. Standard isolation methods include but are not limited to chromatographic methods.

Ginsenosides or the extract containing them according to the invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosol, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive. Preference is given to a topical or orally administration.
Ginsenosides or the extract containing them according to the invention can be converted in a known manner into the usual formulations such as cosmetically, dermatological, pharmaceutical or food supplement compositions. These may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, suppositories, syrups, solid and liquid aerosols, emulsions, pastes, creams, ointments, milks, gels, salves, serums, foams, shampoos, sticks or lotions.

Preference is given to a dermatological or cosmetic composition in a form of an aqueous solution, a white or colored cream, ointment, milk, gel, salve, serum, foam, shampoo, stick, cream, paste, or lotion.

Also preference is given to an orally applicable food supplement composition comprising ginsenosides or the extract containing them according to the invention.

Ginsenosides or the extract containing them according to the invention can be further combined with any other suitable additive or pharmaceutically acceptable carrier, preferably dermatological and/or cosmetically acceptable carrier. Such additives include any of the substances already mentioned, as well as any of those used conventionally, such as those described in Remington: The Science and Practice of Pharmacy (Gennaro and Gennaro, eds, 20th edition, Lippincott Williams & Wilkins, 2000); Theory and Practice of Industrial Pharmacy (Lachman et al., eds., 3rd edition, Lippincott Williams & Wilkins, 1986); Encyclopedia of Pharmaceutical Technology (Swarbrick and Boylan, eds., 2nd edition, Marcel Dekker, 2002). These can be referred to herein as "pharmaceutically acceptable carriers" to indicate they are combined with the active drug and can be administered safely to a subject for therapeutic purposes.

The dosage of ginsenosides or the extract containing them of the present invention can be selected with reference to the effects to be treated and/or the type of disease and/or the disease status in order to provide the desired therapeutic activity. These amounts can be determined routinely for a particular patient, where various parameters are utilized to select the appropriate dosage (e.g., type of disease, age of patient, disease status, patient health, weight, etc.), or the amounts can be relatively standard.

The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.
Preference is given to a composition containing an extract according to the invention in an amount of more than 0.01% up to 10% by weight of the total composition.

Furthermore the composition according to the invention preferably contains G-Rbl in an amount of from 0.001 to 6%, G-RgI in an amount of from 0.001 to 6%, G-Rd in an amount of from 0 to 1.5%, N-Rl in an amount of from 0 to 1.5% and/or G-Re in an amount of from 0 to 1% by weight of the total composition.

The composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to a topical or orally administration.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour toward the active ingredient, type of preparation and time or interval over which the administration is effected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

Ginsenosides or the extract containing them according to the invention can also be combined with at least one further active substance or plant extract e.g. substances or plant extracts usually employed for dermatological use.

Further active substances include but are not limited to desquamating and/or moisturizing agents, UV filtering or blocking agents, depigmenting or propigmenting agents, antiglycation agents, anti-inflammatory agents, anti-microbial agents, agents stimulating the synthesis of dermal, epidermal, hair or nail macromolecules and/or preventing the degradation thereof, agents stimulating the differentiation of keratinocytes, muscle relaxants, antipollution and/or anti-free radical agents, slimming agents, agents acting on the microcirculation, agents acting on the energy metabolism of the cells, tightening agents, agents preventing the loss or stimulating the growth of hair, agents preventing grey or white hair, or a mixture thereof. Preferably that combination is contained in a topically dermatological or cosmetically composition.

Ginsenosides or the extract containing them according to the invention can also be combined with an alpha-hydroxy acid, a salicylic acid or derivatives thereof such as acetylsalicylic acid, a cystein derivative, a ceramide, a steroid, tocopherol, tocotrienol, arbutin or derivatives thereof, ascorbic acid or a derivative thereof, retinol or derivatives thereof, retinoid or derivatives thereof, a carotenoid, glycyrrhetinic acid, glycyrrhizic acid or its salts, a centella extract or isolated ingredients thereof, a plectranthus extract, a boswellia extract, a ginger extract, an aloes extract, an
angelica extract, an eleutherococcus extract, a rhodiola extract, an hippophae extract, a cyanotis extract, a vegetable oil, an oligopeptide, coenzyme Q10, ubiquinone, caffeine, theophylline, a tea extract, a cacao extract, a yeast extract, a soybean extract, a resveratrol and/or a procyanidin oligomer. Preferably that combination is contained in a topically dermatological or cosmetic composition.

Ginsenosides or the extract containing them according to the invention can also be combined with an agent for supporting the cosmetic qualities of skin and/or hair, supporting to stay slim, retaining muscular strength, improving memory, reducing cholesterol, reducing menopause side effects, preventing harmful effects of sunlight and/or preventing cardiovascular problems. Preferably that combination is contained in an orally applicable composition.

Ginsenosides or the extract containing them according to the invention can also be combined with polyunsaturated fatty acids or derivatives thereof, vitamins, oligoelements, a calcium salt, a carotenoid, a phytohormone, a polyphenol, a medicinal plant extract, a carnosine and/or caffeine. Preferably that combination is contained in an orally applicable composition.

Ginsenosides or the extract containing them according to the invention can be used in the field of food supplement or in the dermatological field, which include cosmetically and pharmaceutically use, for the protection of the skin against deleterious effects of stress or irradiation e.g. sunlight or UV irradiation, preferably UV-A or UV-B irradiation.

Protection of the skin according to the invention include but is not limited to protection of the immune system of the skin, protection of the skin against oxidative or other stress, protection against inflammatory skin diseases, protection against apoptosis, protection against senescence, protection against hyperproliferation of skin cells and protection against imperfectly controlled respiration in mitochondriae.

Furthermore ginsenosides or the extract containing them according to the invention can be used for the protection of Langerhans cells, inducing an increase of HO-1 m-RNA expression in human skin fibroblasts, increasing the endogenous synthesis of heme oxygenase, increasing the endogenous production of carbon monoxide and bilirubin, preventing and/or limiting endogenous reactive oxygen species and/or eliminating reactive oxygen species from cells, preventing and/or limiting the photoimmunodepression in the skin e.g. caused by UV light exposure, preventing and/or limiting cellular apoptosis, senescence or loss of functionality of the cells, and/or for the treatment or prevention of diseases or conditions affected thereby.
Furthermore the ginsenosides or the extract containing them according to the invention can be used for wound healing, for skin regeneration and against skin aging.
Examples

Example 1:

Roots or rhizomes of Panax notoginseng are extracted with ethanol. The fraction containing the ginsenosides is isolated by column-chromatography before spray-drying. The corresponding product is in powder form and contains more than 90% of ginsenosides. The purity can be controlled by HPLC and shows extracts which can contain 10 - 60% of G-RbI, 10 - 60% of G-RgI, 0 - 15% of G-Rd, 0 - 15% of N-Rl and 0 - 10% G-Re by weight of the total extract.

Example 2:

The activity of the Panax notoginseng extract (according to Example 1) is evaluated in an ex vivo human skin model against UV-induced Langherans cell toxicity. Skin punches are taken from abdominal skin biopsy and cultured in a medium composed by DMEM, Glutamine, penicillin-streptomycin and fetal calf serum. The Panax notoginseng extract diluted in DMSO is added in the culture medium twice, 24h and one hour before UV-irradiation. Two other biopsies series without any treatment and with or without irradiation are prepared as controls with or without UV. Langherans cells are then specifically labelled by AntiCDla-FITC antibodies. Skin biopsies are frozen and sliced off. Then the sections are observed in epifluorescence in order to count the fluorescent Langherans cells.

The percentage of protection is calculated compared to control without UV according to the following formula:

\[ P\% = \frac{(\text{Control}_{+\text{uv}} - \text{Treated}_{-\text{uv}})}{\text{Control}_{-\text{uv}}} \times 100 \]

In the control + UV the number of Langerhans cells located in the epidermis decreases by 95% and are labelled. A 24 h prior incubation with 0.04, 0.2 and 1 mg/ml of a Panax notoginseng root ginsenoside fraction prevents 32%, 55% and 63 % of the decrease of Langerhans cells.

As the Panax notoginseng extract (according to Example 1) does not absorb UV A or UVB, the tested activity on Langherans cells is indeed linked to biological activity.
Example 3:

Gene expression is measured on cultivated human skin fibroblasts by cDNA array. Panax notoginseng extract (according to Example 1) is added at 0.2 mg/ml in DMSO to a monolayer culture. The test compound and the cells are incubated for 24h in an assay medium. The analysis of genes expression is performed using standard minichips. The chips are spotted using a spotting device and cDNAs specific markers of interest.

It is found by a c-DNA array that the expression of the Heme Oxygenase-1 m-RNA is enhanced to 189% of the base level by a treatment with the ginsenoside fraction of Panax Notoginseng.

Example 4:

Activation of Heme-Oxygenase 1 by Panax notoginseng extract (according to Example 1) is determined by PCR (Polymerase Chains Reaction) amplification. Fibroblasts are cultured in an assay medium containing or not the test compound for 4 h, 8 h or 24 h. At the end of each incubation time, the cells are washed in PBS buffer, placed in Tri-reagent and frozen with G3PDH as reference.

The PCR is performed in triplicate using the LightCycler® system. The incorporation of fluorescence in amplified DNA was measured continuously during the PCR cycles. The 'fluorescence intensity' versus 'PCR-cycle' plot allows the evaluation of a relative expression value for each marker.

The expression of HO-I m-RNA in the cells after 4 h of contact with the P.Notoginseng extract is 313 % of the base level.

Example 5:

The evaluation of the protective effect of the Panax notoginseng extract (according to Example 1) against stress-induced premature senescence is tested in vitro on cultured human diploid fibroblasts. Stress-induced premature senescence can be defined as the long term effects of subtoxic stress on proliferative cell types and can be represented in vitro by \( \text{H}_2\text{O}_2 \) induction. The senescence-associated \( \beta \)-galactosidase is regarded as the biomarker of senescent, non-proliferative cells.
In the present study the fibroblasts treatment happens in 3 phases. In phase 1 fibroblasts are treated for 24 h with the culture medium containing the Panax notoginseng extract at three different concentrations of 50, 150 or 300 µg/ml (pre-treatment phase). Thereafter in phase 2 the medium is changed by a medium containing \( \text{H}_2\text{O}_2 \) (200 µM) for the stress induction. After 2 h the medium is changed again by the initial culture medium having again the three different concentrations of 50, 150 or 300 µg/ml (phase 3, recovery period). After 72 h recovery time the senescence-associated \( \beta \)-galactosidase is determined at pH 6 by colorimetric and fluorimetric tests.

According to the results exposure of fibroblasts to sub-toxic \( \text{H}_2\text{O}_2 \) dose leads to an increase of the amount of \( \beta \)-galactosidase positive cells from 17.6% to 43.5%. A concentration of 150 or 300 µg/ml in the culture medium 24 h before induction and after the period of recovery after the stress significantly decreases the percentage of stress-induced \( \beta \)-galactosidase positive cells, respectively to 37.5% and 33.2%.

Example 6: Tonifying cream

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<th>INCI Name</th>
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<tr>
<td>Isononyl Isononanoate</td>
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</tr>
<tr>
<td>Myristyl Alcohol (and) Myristyl Glucoside</td>
<td>3.00</td>
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<tr>
<td>Cyclomethicone</td>
<td>3.00</td>
</tr>
<tr>
<td>Glyceryl Stearate (and) PEG-100 Stearate</td>
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</tr>
<tr>
<td>Dicapryllyl Ether</td>
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<tr>
<td>C12/15 Albyl Benzoate</td>
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<tr>
<td>Glycerin</td>
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<tr>
<td>Propylene Glycol</td>
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<tr>
<td>Ginsenosides (According to example 1)</td>
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<tr>
<td>Carbomer</td>
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</tr>
<tr>
<td>Xanthan gum</td>
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<tr>
<td>Sodium Hydroxyde</td>
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<td>Water</td>
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What is claimed is:

1. Use of ginsenosides and/or a plant extract containing them for the manufacture of a composition for the protection of the skin against deleterious effects of stress or irradiation.

2. Use of claim 1 wherein the irradiation is sunlight, UV-A or UV-B radiation.

3. Use of claim 1 for the protection of Langerhans cells, inducing an increase of HO-1 mRNA expression in human skin fibroblasts, increasing the endogenous synthesis of heme oxygenase, increasing the endogenous production of carbon monoxide and bilirubin, preventing and/or limiting endogenous reactive oxygen species and/or eliminating reactive oxygen species from cells, preventing and/or limiting the photoimmunodepression in the skin caused by UV light exposure, preventing and/or limiting cellular apoptosis, senescence or loss of functionality of the cells, and/or for the treatment or prevention of diseases or conditions affected thereby.

4. Use of claim 1 for protection of the immune system of the skin, protection of the skin against oxidative stress, protection against inflammatory skin diseases, protection against apoptosis, protection against senescence, protection against hyperproliferation of skin cells and/or protection against imperfectly controlled respiration in mitochondriae.

5. Use of any of claims 1 to 3 wherein the ginsenoside is selected from the group consisting of ginsenoside G-RaI, G-Ra2, G-Ra3, G-RbI, G-Rb2, G-Rb3, G-Rc, G-Rd, G-Re, G-Rf, G-RgI, G-Rg2, G-Rg3, G-RhI, G-Rh2, G-RsI, G-Rs2, G-Ro, MG-RbI, MG-Rb2, MG-Rc, MG-Rd, Q-RI, N-RI, N-R4, 20 Glc-Rf or a mixture thereof.

6. Use of any of claims 1 to 3 wherein the extract is an extract of Panax notoginseng (San Qi), Panax ginseng (C.A.Meyer) and/or Panax quinquefolium.

7. Use of claim 6 wherein the extract is an extract of the roots or the rhizomes.

8. Use of any of claims 1 to 7 wherein the extract contains ginsenosides in an amount between 0.1% and 100% by weight of the total extract.

9. Use of any of claims 1 to 8 wherein the extract contains ginsenosides in an amount of equal or more than 80% by weight of the total extract.

10. Use of any of claims 1 to 9 wherein the extract contains G-RbI in an amount of from 10 to 60%, G-RgI in an amount of from 10 to 60%, G-Rd in an amount of from 0 to 15%, N-RI...
in an amount of from 0 to 15% and/or G-Re in an amount of from 0 to 10% by weight of the total extract.

11. Use of any of claims 1 to 10 wherein the composition contains ginsenosides in an amount of from 0.01% up to 10% by weight of the total composition.

12. Use of any of claims 1 to 11 wherein the composition contains G-RbI in an amount of from 0.001 to 6%, G-RgI in an amount of from 0.001 to 6%, G-Rd in an amount of from 0 to 1.5%, N-RI in an amount of from 0 to 1.5% and/or G-Re in an amount of from 0 to 1% by weight of the total composition.

13. Use of any of claims 1 to 12 wherein the ginsenosides or the extract containing them is combined with at least one further active substance or plant extract.

14. Use of claim 13 wherein the ginsenosides or the extract containing them is combined with at least one further active substance or plant extract usually employed for dermatological use.

15. Use of any of claims 1 to 14 wherein the composition is a dermatological or cosmetical composition for topical administration.

16. Use of any of claims 1 to 15 wherein the composition is a liquid solution or a cream.

17. Use of any of claims 1 to 13 wherein the composition is a food supplement.

18. Use of claim 17 wherein the composition is a normal or enteric coated tablet, capsule, pill, granule, elixir, solution or suspension.
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K36/258

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)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>CURRI S B ET AL: &quot;DERMOCOSMETIC ACTIVITY OF GINSENOSES. NOTE III. LONG TERM EVALUATION OF THE MOISTURIZING AND TONIFYING EFFECT ON THE FACE SKIN&quot; FITOTERAPIA, IDB HOLDING, MILAN, IT, vol. 57, no. 4, 1986, pages 217-222, XP001147161 ISSN: 0367-326X the whole document</td>
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<td>DATABASE TCM [Online] SIPO; 3 September 1997 (1997-09-03), ZHANG QI: &quot;Natural ginseng skin-care liquid and its production method&quot; XP002442516 Database accession no. CN-96120934-A abstract</td>
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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

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on the novelty of or claims(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

Date of the actual completion of the international search

20 August 2007

Date of mailing of the international search report

12/09/2007

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

THALMAIR, M

Form PCT/ISW210 (second sheet) (April 2005)
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<td>PANWAR MEENAKSHI ET AL: &quot;Evaluation of chemopreventive action and antimutagenic effect of the standardized Panax ginseng extract, EFLA400, in Swiss albino mice&quot; PHYTOTHERAPY RESEARCH, JOHN WILEY &amp; SONS LTD. CHICHESTER, GB, vol. 19, no. 1, January 2005 (2005-01), pages 65-71, XP009086394 ISSN: 0951-418X page 67</td>
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<td>KONOSHIMA TAKAO ET AL: &quot;Anti-tumor-promoting activities of the roots of Panax-notoginseng (1)&quot; NATURAL MEDICINES - SHOYAKUGAKU ZASSHI, JAPANESE SOCIETY OF PHARMACOGNOSY, TOKYO, JP, vol. 50, no. 2, 1996, pages 158-162, XP009086400 ISSN: 1340-3443 page 158, left-hand column - page 159, left-hand column, last paragraph</td>
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<td>SCAGLIONE F ET AL: &quot;The standardised G115(R) Panax ginseng CA. Meyer extract: A review of its properties and usage&quot; 2005, EVIDENCE-BASED INTEGRATIVE MEDICINE 2005 NEW ZEALAND, VOL. 2, NR. 4, PAGE(S) 195-206 , XP001536601 ISSN: 1176-2330 1176-2330 the whole document</td>
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INTERNATIONAL SEARCH REPORT

Box H  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. [X] 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.

   see FURTHER INFORMATION sheet PCT/ISA/210

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 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:

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 an additional fee, this Authority did not invite payment of any additional fee.

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.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
Continuation of Box II.2

Claims Nos.: 3

The subject-matter of claim 3 is not considered as being clear, since it is not clear which diseases or conditions are affected by protection of Langerhans cells, inducing an increase of HO-I m-RNA expression in human skin fibroblasts, increasing the endogenous synthesis of heme oxygenase, increasing the endogenous production of carbon monoxide and bilirubin etc.. Therefore, the skilled person does not know how many and which specific medical conditions are met by the phrasing of claim 3. Hence, the subject-matter of this claim was not searchable.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
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<tbody>
<tr>
<td>CN 1158247 A</td>
<td>03-09-1997</td>
<td>NONE</td>
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