

NOVEL SKIN CARE FORMULATION**CROSS REFERENCE TO RELATED APPLICATION**

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/872,784, entitled "Novel Skin Care Formulation" and filed on September 2, 2013, which is incorporated herein by reference.

RELATED ART

[0002] Many consumers are concerned with the physical characteristics of their skin. For example, consumers with wrinkles, dry spots or sun damage often wish for such features to be less pronounced. Many portions of a person's skin are in constant interaction with external stimuli and are affected by environmental factors such as sun and wind exposure. This exposure can result in physical and visible changes to the skin. In addition, certain physical conditions, such as disease, may affect the appearance of the skin.

[0003] Cobra venom has found extensive use as a therapeutic primarily for pain relief. Clinical investigations from the 1930's through the 1950's revealed that cobra venom is a potent pain killer with activity superior to morphine, but without the known adverse effects of opiates. In the United States, cobra venom for medicinal use is only available in the form of homeopathic products that contain extremely low concentrations of the active product. In homeopathy, the preferred dilution of cobra venom is a 1:10,000 dilution, although the volume actually administered has been quite variable over the years. Present guidelines, as provided in the Homeopathic Pharmacopoeia of the United States (USHP), list the recommended dilutions in the range of 10^{-6} to 10^{-8} .

[0004] The use of cobra venom as a treatment for pain and disease was utilized in the 1930's following research and clinical studies that revealed that cobra venom had very potent analgesic activity. However, during this period cobra venom was

administered only by injection. While clinically successful and safe, it required frequent injections of cobra venom by physicians and this method of administration fell out of favor by the 1970's.

[0005] Silicon is an essential element for life. It has both a structural role being a constituent of the proteins-glycosaminoglycanes complexes found in the connective tissue matrix, and a metabolic role on growth and osteogenesis (silicon favors the process of mineralisation of the bone). Silicon is naturally present in food as a silicon dioxide (SiO_2), free orthosilicic acid (H_4SiO_4), silicic acids bound to certain nutrients, and in the silicate form. In order to be adsorbed efficiently silicon must be hydrated in the form of orthosilicic acid (H_4SiO_4). Orthosilicic acid polymerizes at neutral pH (7.0-8.0) and remains as a monomeric molecule at low and high pH. As a polymer it is insoluble in water and therefore poorly adsorbed. Within the host the orthosilicic remains in a monomeric form presumably because it associates with other plasma components such as proteins and carbohydrates. Proteins combine with orthosilicic acid mainly through their amino groups but subsidiary links, such as hydrogen bonds and the van der Waals forces, may have also been involved. Orthosilicic acid has been found to have anti-wrinkle effects, prevent the loss of moisture through the skin and stimulate collagen production.

DETAILED DESCRIPTION

[0006] As required, detailed embodiments of the present disclosure are described herein; however, it is to be understood that the disclosed embodiments are merely exemplary of the disclosure which may be embodied in various forms. Therefore, specific functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims to be later appended and as a representative basis for teaching one skilled in the art to variously employ the present disclosure in virtually any appropriate circumstance.

[0007] The present disclosure generally pertains to compositions and methods for the treatment and care of skin, especially to the treatment of dehydrated and damaged skin associated with environmental exposure and disease. The inflammation associated with dermatological or immunological conditions, rheumatoid arthritis, viral and bacterial infections, and lesions may also respond to treatment with the present formulations. The formulation consists of a mixture of cobra venom and orthosilicic acid (OSA) with an acceptable excipient for either oral or topical administration. Prior administration of cobra venom and OSA has been accomplished through multiple injections. These injections cause pain and discomfort for the subject and require continued medical supervision. The present disclosed oral and topical formulations eliminate these disadvantages.

[0008] As used herein, the term "about" means approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

[0009] As used herein, the term "administer" means the act of delivering or applying a skin care formulation of the present disclosure to a subject. For example, administration of the formulation to a subject includes, but is not limited to, oral consumption or topical application.

[0010] As used herein, the term "base" means a pharmaceutically acceptable carrier which does not interfere with effectiveness of the formulation and that is not toxic to the subject to which it is administered. Such bases may include lotions, creams, or aqueous solutions.

[0011] As used herein, "dose" or "dosage" means a specified quantity of a formulation of the present disclosure provided in a single administration or over a specified amount of time. Dose may be determined based on recommendations provided by healthcare experts and researchers.

- [0012] As used herein, the term "excipient" means an additive included in the final dosage vehicle of the skin care formulation. Excipients provide physical and/or aesthetic properties of the dosage vehicle for delivery of the formulation to the desired target location. An excipient may be included for the purpose of bulking-up the formulation (and may also be referred to as a "bulking agent," "filler," or "diluent"), or to confer a therapeutic enhancement in the final dosage form, such as facilitating drug absorption or solubility.
- [0013] As used herein, the term "formulation" means a preparation suitable for oral or topical administration to a subject.
- [0014] As used herein, the term "subject" means any and all organisms. "Subject" may refer to a human or any other animal.
- [0015] Technical and scientific terms used herein have the meaning commonly understood by one of skill in the art to which the present disclosure pertains, unless otherwise defined. Reference is made herein to various methodologies and materials known to those of skill in the art. Any suitable materials and/or methods known to those of skill in the art can be utilized in carrying out the present disclosure. However, preferred materials and methods may be described.
- [0016] Many factors may contribute to the change in the cosmetic appearance of the skin. These factors may include, for instance, injury, disease, age, environmental exposure, changes in hormone levels, externally applied or ingested materials such as medications, genetic conditions or a combination of these and other factors. Changes in the appearance of the skin may be seen as irregularities or abnormalities, for instance drying, wrinkling, sagging or changes in pigmentation.
- [0017] The formulations of the present disclosure include cobra venom. *Naja* is a genus of venomous elapid snakes known as cobras which includes 28 species. Members of the genus *Naja* are the most widespread and the most widely recognized as cobras. Several other genera include species commonly referred to as cobras. One example is the *Ophiophagus hannah* species, commonly referred to as the king cobra.

Various cobra species occur in regions throughout Africa, Southwest Asia, South Asia and Southeast Asia. In one embodiment of the disclosure, the cobra venom may be isolated from the *Naja* and the *Ophiophagus hannah* species. Other types of cobra venom may be used in other embodiments. In one embodiment, the cobra venom of the present disclosure demonstrates both analgesic and anti-inflammatory properties. In an additional embodiment, the formulations of the present disclosure include non-synthetic peptides and neuropeptides native to the king cobra venom.

[0018] The formulations of the present disclosure further include orthosilicic acid. Orthosilicic acid has been shown to promote collagen formation in cartilage. In one embodiment, the orthosilicic acid of the presently disclosed formulations is in the hydrated form (H_4SiO_4) and is thus absorbed effectively by the subject.

[0019] In one embodiment, the cobra venom/OSA formulations of the present disclosure may be formulated in a wide variety of oral administration dosage forms. Oral administration can be in the form of tablets, coated tablets, dragees, hard and soft gelatin capsules, solutions, emulsions, syrups, or suspensions.

[0020] In this embodiment, oral administration is generally accomplished using a convenient daily dosing regimen which can be adjusted according to the degree of affliction and the subject's response. The cobra venom and the OSA of the present disclosure, together with one or more conventional excipients, may be placed into the form of pharmaceutical compositions and unit dosages. The formulations may be employed as solids, such as tablets or filled capsules, semisolids, powders or sustained release formulations. In an additional embodiment, the formulations may be employed as liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use, in the form of suppositories for rectal or vaginal administration.

[0021] The cobra venom and OSA oral formulations of this disclosure can be administered alone but will generally be administered in admixture with one or more suitable excipients with regard to the intended route of administration and standard pharmaceutical practice. Such excipients may include, for example, diluents or fillers,

binders, disintegrants, lubricants, coloring agents, flavoring agents, solubilizers, suspending agents and preservatives. In one embodiment, the excipient used with the present oral formulations includes water, a sweetener, preservatives and a pH modifier. The concentrations of these ingredients will be known to one of skill in the art.

[0022] In one embodiment, solid form preparations (including powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules) may include one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Powders formulations may include a finely divided solid which is a mixture with the finely divided active component.

[0023] In an additional embodiment, the liquid cobra venom/OSA formulation preparations of the present disclosure may comprise emulsions, syrups, elixirs, aqueous solutions and aqueous suspensions. These preparations may include solid form preparations which are intended to be converted to liquid form preparations shortly before use. Emulsions may be prepared in solutions, for example, in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the cobra venom and OSA in suitable excipients, including water and adding suitable colorants, flavors, stabilizing, and thickening agents.

[0024] In an additional embodiment, the formulations of the present disclosure may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with excipients (also referred to as a "base") such as an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with excipients such as an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and

acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0025] In one embodiment, the formulations of the present disclosure may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

[0026] In an additional embodiment, the formulations of the present disclosure may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays are known in the art to be appropriate.

[0027] The formulations of the present disclosure may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example, with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the subject administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomizing spray pump. In an additional embodiment, the formulations of the present disclosure may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration.

[0028] When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the cobra venom and OSA. For example, the formulations of the present disclosure can be prepared in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the cobra venom and OSA is necessary and when patient compliance with a treatment regimen is crucial.

[0029] The modification of the present formulations to render them more soluble in water or other vehicle, for example, may be easily accomplished by minor modifications

(salt formulation, esterification, etc.), which are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular formulation in order to manage the pharmacokinetics of the present formulations for maximum beneficial effect in patients.

[0030] The term "therapeutically effective amount" as used herein means an amount required to reduce symptoms of a condition in a subject. The dose will be adjusted to the individual requirements in each particular case. That dosage can vary within wide limits depending upon numerous factors such as the severity of the condition to be treated, the age and general health condition of the subject, other medicaments with which the subject is being treated, and the route and form of administration of the formulation.

[0031] For oral administration, the daily dosage of cobra venom will be from about 35 µg to about 300 µg of cobra venom per day and about 0.1 mg to about 1.5 mg OSA per day. In one embodiment, the daily dosage comprises about 70 µg of cobra venom and about 200 µg of OSA per day. For oral administration, the formulation will contain from about 10 µg/ml to about 1.0 mg/ml cobra venom and from about 200 mg/ml to about 2.0 mg/ml OSA. In an additional embodiment, the concentration of cobra venom is about 50 µg/ml and the concentration of orthosilicic acid is about 1.0 mg/ml. The rate of administration of the oral formulations (*i.e.*, the number of administrations per day) may vary depending on the severity of the condition to be treated. For topical administration, the formulation will contain from about 5.0 µg to about 1.0 mg of cobra venom per gram of base and about 2 µg to about 0.2 mg of OSA per gram of base. In one embodiment, the concentration of the formulation is 10 – 30 µg of cobra venom per gram of base and about 50 µg of OSA per gram of base. The number of dosage administrations per day, and the length of administration (*i.e.*, the number of days the oral dose is administered) will depend of the severity of the condition to be treated and the effectiveness of the formulation. One of ordinary skill in treating conditions described herein will be able, without undue experimentation and in reliance on personal knowledge, experience and

the disclosures of this application, to ascertain a therapeutically effective amount of the formulations of the present disclosure for a given disease and subject.

[0032] The current disclosure provides a method for treating a skin, inflammatory or autoimmune condition comprising administering to a subject in need thereof a therapeutically effective amount of the cobra venom/OSA formulations described herein. In one embodiment, the method comprises oral administration of the formulation. In an additional embodiment, the method comprises topical administration of the formulation. In an additional embodiment, the condition is rheumatoid arthritis.

[0033] The disclosure further provides a method for treating a skin, inflammatory or autoimmune condition comprising administering to a patient in need thereof a therapeutically effective amount of cobra venom/OSA formulations described herein. In one embodiment, the method comprises oral administration of the formulation. In an additional embodiment, the method comprises topical administration of the formulation. In an additional embodiment, the condition is rheumatoid arthritis.

[0034] The current disclosure provides the use of the cobra venom/OSA formulations described herein for the manufacture of a medicament useful for treating a skin, inflammatory or autoimmune condition. In one embodiment, the method comprises oral administration of the formulation. In an additional embodiment, the method comprises topical administration of the formulation. In an additional embodiment, the condition is rheumatoid arthritis.

[0035] Examples

[0036] The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present disclosure. They should not be considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof. Preparative Examples

[0037] ANIMAL STUDIES

[0038] Experiment 1

[0039] A tolerance study was undertaken to observe the allergic reactions of guinea pigs to a topical gel formulated with cobra venom. This animal model attempts to sensitize the host to the test product over a two-week period, followed by a challenge two weeks later. The test animals (guinea pigs) were depilated over a 3 X 4 cm area on their back and treated with repeated topical application of the test substances: native cobra venom, modified cobra venom, gel without actives and 0.1% 2, 4-dinitro-chlorobenzene solution at days 1, 7, and 14. On day 28, each animal was treated with 1% 2,4-dinitrochlorobenzene solution on the opposite side where a depilated area of 3 X 4 cm was prepared. Allergy reactions were observed and recorded at 0, 24, 48 and 72 hours, along with skin allergy reaction strength.

[0040] The data obtained during this study demonstrated that neither the topical cobra venom formulations nor the excipients induced localized allergic reactions.

[0041] Experiment 2

[0042] A gel formulation was tested in the mouse formalin paw assay to validate the pharmacodynamic activity of topical cobra venom. This assay acts as model for analgesia and inflammation to assess the local effects of the drug. Here, mice were divided into a control group and a treatment group (each group >10 animals). The cobra venom gel was applied directly to the mouse's right rear paw for three days, once a day at a concentration of 20 µg/g of base. A 1.5% formalin solution was injected into the mice's right posterior paw on the fourth day, 5 hours after application of the drug. The mice were observed for paw licking as a reaction to the pain. The licking paw time was recorded from 0-5 minutes as phase 1 and 15-30 min as phase 2. Similar study groups were developed to assess the systemic activity of the cobra venom gel. In this

procedure the cobra venom formulation was applied to a depilated section on the back of the animal.

[0043] The cobra venom formulation was poorly effective by local and systemic applications in the phase 1 component while significantly active in the phase 2 stage. However, the analgesic activity was not clearly dose responsive though both local and distant modes of application were surprisingly effective. This result indicates that the venom can influence the pathways associated with the perception of pain and inflammation.

[0044] Experiment 3

[0045] An adjuvant arthritis model was undertaken to determine if the reported anti-inflammatory and disease modifying activity of cobra venom could be achieved by oral administration. The dose ranges selected for this study were empirically chosen to simulate maximum tolerable clinical dosing by injection (2-4 mg) and reported oral doses (6.5 mg) used in rudimentary homeopathic applications. In addition, a high dose was tested, with concentrations approximately equating to 30 mg/kg, 90 mg/kg and 270 mg/kg of animal weight. Experimental groups of eight rats were selected to include untreated control, CFA only control, cobra venom at doses of 30, 90, and 270 µg/kg. The animals received test substances by intragastric administration daily at 9 AM. The inhibitory effects on acute inflammation in an animal model were then tested. Edema was induced by the subcutaneous injection of 0.1 mL of CFA into the right hind paw on day 5, six hours after morning dosing. The animals received the test substances daily until day 28, starting at 9 am of day 11 after induction, to examine the effects for an extended period (i.e., chronic effects).

[0046] These results fully demonstrate that orally administered cobra venom is effective in this animal model of RA arthritis, exerting the same dose dependent immunomodulatory and joint protective effects reported for cobra venom by injection. Contrary to previous studies, the proteins present in the cobra venom solution (i.e., the

non-synthetic peptides and neuropeptides) were biologically effective through oral administration.

[0047] The foregoing studies support the use of a combination cobra venom/OSA formulation in oral and topical formats, a major advancement over the injectable product formally known as Nyloxin. These formulations eliminate the need for injections in addition to bypassing the discomfort and medical supervision associated with parenteral administration.

[0048] HUMAN STUDIES

[0049] Experiment 1

[0050] A topical formulation was prepared consisting of 0.02mg cobra venom per gram of base and 0.05mg OSA per gram of base. The formulation was supplied to several subjects to assess the effects when applied to the face and neck.

[0051] Subject 1. Female subject with aged skin

[0052] A female, aged 55, assessed the topical formulation over the course of a few months. No adverse effects were reported. The subject felt that the product left her skin feeling hydrated and the tiny lines seems diminished around her eyes and mouth.

[0053] Subject 2. Female subject with aged skin

[0054] A female, aged 63 assessed the topical formulation over the course of a few months. She was a frequent user of other skin care products but found them unsatisfactory. No adverse effects were reported. She found that after several weeks, many of the small lines around her lips and eyes began to disappear. She also used the formulation on her neck and a deep wrinkle there began to diminish significantly. With prolonged use her skin continued to become more even and smooth. She extended the use of the formulation to the back of her hands.

[0055] Subject 3. Female subject with aged skin

[0056] A female, aged 51 assessed the topical formulation over the course of a few months. She was also frequent user of other skin care products though without satisfaction. No adverse effects were reported. She noticed positive changes in the tone, elasticity, appearance and overall health of her skin. She felt that the circulation in her skin was enhanced leaving the skin feeling more supple. The lines around her eyes and mouth were less obvious, and the dark areas are much less noticeable. Discontinuation of the use of the formulation for a couple of weeks resulted in a noticeable deterioration in the softness and suppleness that had been previously attained.

[0057] Subject 4. Female subject with normal skin

[0058] A female, aged 26 assessed the topical formulation over the course of a few months to determine its potential to protect the skin. After applying the formulation for about a month, no adverse effects were noted. However, she noticed a dramatic change in the tone and texture of the skin. The subject suffered from rosacea, which would vary in its severity and occasionally result in embarrassing red patches. This rosacea has almost completely disappeared such that the need to camouflage the area with other cosmetics has been eliminated. A reduction in fine lines on the forehead has also been reported.

CLAIMS

Now, therefore, the following is claimed:

1. An orally administrable pharmaceutical formulation, comprising: king cobra venom, orthosilicic acid and an excipient.
2. The formulation of claim 1, wherein the cobra venom comprises *Ophiophagus hannah* venom.
3. The formulation of claim 1, wherein the formulation is a solid form preparation.
4. The formulation of claim 1, wherein the formulation is a liquid preparation.
5. The formulation of claim 1, wherein the concentration of cobra venom is from about 10µg/ml to about 1.0 mg/ml and the concentration of orthosilicic acid is from about 200 mg/ml to about 2.0 mg/ml.
6. The formulation of claim 1, wherein the concentration of cobra venom is about 50µg/ml and the concentration of orthosilicic acid is about 1.0 mg/ml.
7. A topically administrable pharmaceutical formulation, comprising: cobra venom, orthosilicic acid and an excipient.
8. The formulation of claim 7, wherein the cobra venom comprises *Ophiophagus hannah* venom.

9. The formulation of claim 7, wherein the formulation is a lotion preparation.
10. The formulation of claim 7, wherein the formulation is a gel preparation.
11. The formulation of claim 7, wherein the concentration of cobra venom is from about 5.0 μg to about 1.0 mg per gram of base and the concentration of orthosilicic acid is from about 2 μg to about 0.2 mg per gram of base.
12. The formulation of claim 7, wherein the concentration of cobra venom is about 20 μg per gram of base and the concentration of orthosilicic acid is about 50 μg per gram of base.
13. A method of treating a skin, inflammatory or autoimmune condition comprising administering to a subject in need thereof a therapeutically effective amount of the formulation of claim 1.
14. The method of claim 13, wherein the cobra venom comprises *Ophiophagus hannah* venom.
15. The method of claim 13, wherein the condition is rheumatoid arthritis.
16. The method of 13, wherein the formulation is a solid form preparation.
17. The method of 13, wherein the formulation is a liquid preparation.

18. A method of treating a skin, inflammatory or autoimmune condition comprising administering to a subject in need thereof a therapeutically effective amount of the formulation of claim 7.

19. The method of claim 18, wherein the cobra venom comprises *Ophiophagus hannah* venom.

20. The method of claim 18, wherein the condition is rheumatoid arthritis.

21. The method of claim 18, wherein the formulation is a lotion preparation.

22. The method of claim 18, wherein the formulation is a gel preparation.