The present invention relates to botanical Hylotelephium compositions as histamine receptor antagonists for preventing and treating conditions or disorders mediated by histamine receptors. The invention further relates to the methods of manufacture and use thereof.
BOTANICAL COMPOSITION AND METHODS OF MANUFACTURE AND USE

[0001] The present application claims priority to US Application Serial No. 61/365,385 filed July 19, 2010, the entire contents of which are incorporated herein by reference.

[0002] The present invention relates to a botanical composition useful as a histamine receptor antagonist for preventing, treating, or ameliorating the conditions or disorders mediated by histamine receptors. The invention further relates to the methods of manufacture and use thereof.

BACKGROUND OF THE INVENTION

[0003] Histamine is a hydrophilic vasoactive amine, or an important messenger molecule released from mast cells, white blood cells called basophils, enterochromaffin-like cells, and neurons. Histamine plays a pathophysiological regulatory role in cellular events through binding to four types of histamine receptors (i.e. H1R, H2R, H3R and H4R), they being G-protein-coupled receptors with histamine as their endogenous ligand.

[0004] The various biological effects of histamine mediated through the activation of specific histamine H1, H2, H3 and H4 receptors differ in their tissue expression patterns and functions. All four types known histamine receptors (i.e. H1R, H2R, H3R, and H4R) have been used or proposed as therapeutic targets for a wide variety of diseases. Histamine H1 receptor causes systemic vasodilatation, smooth muscle contraction, separation of endothelial cells, potentiation of pain, and pruritus etc. Histamine H2 receptor stimulates gastric acid secretion, regulates gastrointestinal motility and intestinal secretion, and is thought to be associated with regulating cell growth and differentiation. Histamine H3 receptor decreases neurotransmitters (e.g. histamine, etc.) release from the neurons. Histamine H4 receptor has been shown to be involved in chemotaxis and inflammatory mediators release by eosinophils, mast cells, monocytes, dendritic cells, and T cells.

[0005] Histamine receptor antagonists to block action of histamine have found use in therapy for the various diseases, such as allergic and inflammatory conditions,
autoimmune conditions or disorders, gastrointestinal disorders, different diseases associated with abnormal neurotransmitter levels, immune system disorders, and the disorders involved in abnormal cell proliferation including both benign and malignant cells, etc.

However, conventional medicines may often cause uncertain side effects. For example: Loratadine (or Claritin, Claritin RediTabs, etc.), one of histamine H1 receptor antagonists may commonly cause headache, drowsiness, fatigue and dry mouth. In addition, major side effects of Famotidine (i.e. Pepcid, a histamine H2 receptor antagonist) include constipation, diarrhea, fatigue, headache, insomnia, muscle pain, nausea, and vomiting. Additionally, inhaled corticosteroids are first-line agents for conventional treatment in severe acute asthma attacks mediated by histamine receptors; and the administration of corticosteroids and pharmaceutical compositions comprising corticosteroids can promote wound healing and reduce scar formation, as described in international patent application publication WO/2011/006100 Method Of Wound Healing And Scar Modulation. But, long-term use of corticosteroids can have many side effects including thinning of the skin and easy bruising, a redistribution of fat, increased appetite, weight gain, blood glucose problems, insomnia, and emotional changes, etc.

Accordingly, patients may be seeking out alternative treatments to avoid the adverse effects of conventional treatments that can be invasive and expensive, and there is a need in the art for a safe and effective alternative method by which to prevent and/or treat the conditions or disorders mediated by histamine receptors, particularly, natural products for promotion of health as well as treatment of disease.

SUMMARY OF THE INVENTION

In view of the problems related to the known methods and medications used to treat conditions or disorders mediated by histamine receptors, one object of the invention is to provide a botanical agent with diverse bioactive effects for preventing and treating the above conditions or disorders. Advantageously, the compositions of the present invention are relatively inexpensive to manufacture, provide an immediate effects, safe to administer, and easy to apply.
The present invention provides safe and effective botanical agent as histamine receptor antagonists for a subject at risk of or suffering from the conditions or disorders mediated by histamine receptors. The present invention also contemplates administering an effective amount of leaf extract of plant Hylotelephium spectabile (Boreau) H.Ohba (called "Hylotelephium composition" for short hereinafter). The present inventors have found that compositions according to the present invention and including Hylotelephium and the different combination preparations are effective. The efficacy of the present compositions has been established through several trials where compositions including Hylotelephium and delivered orally, topically, or both, and the trial for orally administering Hylotelephium composition to a subject on a regular basis for 72 days (called "Trial I" for short hereinafter).

The term "Trial I" as used in the present specification, refers to a trial conducted by orally administering a Hylotelephium composition to a subject on a regular basis for 72 consecutive days.

The foregoing and other objects, features, and advantages of the botanical agents disclosed in the present invention will become apparent upon further review of the detailed description of preferred embodiments and concrete examples, and it will demonstrate the efficacy of the disclosed composition as histamine receptor antagonists for preventing and treating the said conditions or disorders.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a composition comprising a leaf extract of the plant Hylotelephium spectabile (Boreau) H.Ohba and a use for preventing and treating the conditions or disorders mediated by histamine receptors in a subject.

The plant suitable for use in the present invention is Hylotelephium spectabile (Boreau) H.Ohba (Synonym: Sedum spectabile Boreau or Sedum spectabile Bor.) is called "Hylotelephium spectabile", "Sedum spectabile", or "Hylotelephium" for short hereinafter. Hylotelephium is a succulent herbaceous perennial plant and has the common name of Stonecrop, Showy stonecrop, Ice plant,
Orpine, or Live-Forever, etc. It is also referred to by its Chinese name of "Shi Tou Cai", "Chang Yao Ba Bao", "Chang Yao Jing Tian", or "XTe Zi Zhang", etc. The Hylotelephium useful in the present invention includes, but is not limited to, the varieties, cultivars, hybrids, and other closely related species thereof.

For example: the following related species may be useful in the present invention: Hylotelephium 'Autumn Joy' (Herbstfreude') [Synonym: Sedum 'Autumn Joy' (Herbstfreude ')], Hylotelephium spectabile 'Brilliant' (Synonym: Sedum spectabile 'Brilliant'), Hylotelephium spectabile 'Carmen' (Synonym: Sedum spectabile 'Carmen'), Hylotelephium spectabile 'Iceberg' (Synonym: Sedum spectabile 'Iceberg'), Hylotelephium spectabile 'Meteor' (Synonym: Sedum spectabile 'Meteor'), Hylotelephium spectabile 'Stardust' (Synonym: Sedum spectabile 'Stardust'), Hylotelephium spectabile Variegatum' (Synonym: Sedum spectabile 'Variegatum'), Hylotelephium 'Frosty Morn' (Synonym: Sedum 'Frosty Morn'), Hylotelephium 'Morchens' (Synonym: Sedum 'Morchens'), Hylotelephium 'Rosy Glow' (Synonym: Sedum "Rosy Glow"), and Hylotelephium 'Vera Jameson' (Synonym: Sedum Vera Jameson) (http://web1.msue. msu.edu/imp/modzzy00001350.html), Hylotelephium spectabile (Bor.) H. Ohba var. angustifolium, Hylotelephium spectabile (Bor.) H. Ohba var. spectabile, Hylotelephium angustum (Maxim.) H. Ohba, Hylotelephium bonafousii (Hamet) H. Ohba, Hylotelephium erythrostictum (Miq.) H. Ohba, Hylotelephium ewersii (Lede) H. Ohba, Hylotelephium mingjinianum (S. H. Fu) H. Ohba, Hylotelephium mongolicum (Franch.) S. H. Fu, Hylotelephium pallescens (Freyn) H. Ohba, Hylotelephium pseudospectabile (Praeg.) S. H. Fu, Hylotelephium purpureum (L.) Holub, Hylotelephium sieboldii (Sweet ex Hk.) H. Ohba, Hylotelephium subcapitatum (Hayata) H. Ohba, Hylotelephium tatarinowii (Maxim.) H. Ohba, Hylotelephium tatarinowii (Maxim.) H. Ohba var. integrifolium, Hylotelephium tatarinowii (Maxim.) H. Ohba var. tatarinowii, Hylotelephium verticillatum (L.) H. Ohba, and Hylotelephium viviparum (Maxim.) H. Ohba, etc. (http://db. kib.ac.cn/eflora/view/search/chs_contents. aspx?l_name=Hylotelephium%20H.%20Ohba).

The particularly preferred plant is Hylotelephium spectabile (Boreau)
H.Ohba (For a photograph, please see: http://www.zhiwutong.com/dan_tu/70/56014.htm), the contents of which is incorporated herein by reference.

**Publications Illustrating Effects of *Hylotelephium Spectabile* (Boreau) H.Ohba on Health**

[0016] The plant *Hylotelephium spectabile* (Boreau) H.Ohba, i.e. *Hylopectelium spectabile* or *Sedum spectabile*, is documented in the Southeast Asian botanical literature as either a food or a medicinal plant. In particular, the leaves may be eaten as food, and the plant was plentiful so the leaves were fed to pigs in Laos. *Hylopectelium spectabile*, often combined with Angelica, is used as a seasoning for chicken or cooked with eggs when prepared as a tonic besides as a medicine for sores or upset stomach; and is thought to help a weak person regain strength when cooked with a freshly killed chicken [Corlett, Jan L et al. (2003), "Hmong Gardens: Botanical Diversity in an Urban Setting." Economic Botany 57(3):365-379].

[0017] It is reported that the exotic culinary and medicinal herbs grown by Hmong refugees in Sacramento, California included herb leaves, or infusions of steamed herb leaves were widely consumed as a component of pregnancy and post-partum diets; six common species, Acorus gramineus ..., and Sedum aff. spectabile were used in combination to season chicken (Corlett JL, et al., "Mineral Content Of Culinary And Medicinal Plants Cultivated By Hmong Refugees Living In Sacramento, California" Int J Food Sci Nutr. 2002 Mar; 53(2): 117-28).

[0018] According to the ethnobotanical data from Duke's Phytochemical and Ethnobotanical Databases, *Hylotelephium spectabile* is used to treat abscess, alexiteric, erysipelas, inflammation, sialogogue, sore (throat), swelling, thirst, and Trauma (See: http://www.ars-grin.gov/cgi-bin/duke/ethnobot.pl?Sedum%20spectabile).

[0019] In the "Chinese Materia Medica", *Hylotelephium spectabile* (Boreau) H.Ohba with Chinese name of "Shi Tou Cai" is documented as follows: functions and indications, clearing heat and detoxicating, relieving swelling and pain, treating
furuncle, carbuncle, empyrosis, burn, and bee sting (See: http://www.zhzyw.org/zycs/zycd/s/0951910KJEBECFG6IAFIB2BF.html).

Moreover, the research indicated that Sedum spectabile Bor. functions in the facultative Crassulacean acid metabolism (CAM) mode (C3 is planted in spring, CAM is planted in summer). In accordance with the research, C3 plants take up exclusively CO₂ needed for photosynthesis in the light whereas CAM plant take up the CO₂ mainly in the dark, which means the plant Sedum spectabile Bor. has typical C3-activity in spring and has typical CAM-activity in summer [Claus Buschmann, et al, "Changes of the chlorophyll fluorescence induction kinetics of C3 and CAM plants during day/night cycles." Photosynthesis Research 4, 337-349 (1983) (See: http://www.springerlink.com/content/t1075h4060105662/fulltext.pdf?page=1)].

International Patent Publication WO/2002/005830 Extracts From Crassulacean Acid Metabolism (Cam) Mechanism Plants And Uses Thereof summarizes the common uses of CAM plants in Table 1, for example, Sedum sp. Anti-inflammatory.

United States Patent Application 20040156920 "Extracts from plant and non-plant biomass and uses thereof describes that: CAM plants have been used for many human applications. Most often, plant parts, such as leaves, or plant juices are orally administered.

"Sedoheptose, a new sugar from Sedum spectabile." J Biol Chem 30: 61-77 (or see: http://www.jbc.org/content/30/1/61.full.pdf+html).

Patent CN 1110303C (Application Number: 99112550, Publication Number: 1277020) "Application of hylotelephin to the production of anti-virus new drugs" (i.e. "Application of Eight precious extract in preparing antiviral medicine") discloses as follows: Sedoheptulose anhydride is first extracted from crassulaceae plant and then condensed with acetone to obtain one kind of compound with antiviral activity. The compound, structural tests show, is isopropylidene sedoheptulose anhydride and is named as Eight Precious Extract. It may be used in preparing medicine for resisting hepatitis B virus (See: http://www.chemyq.com/patentfmen/pt34/331552_F1CF3.htm).

United States Patent Application 20090239812 Use Of C7 Sugars In Prevention And Treatment Of Mycoses describes that D-mannoheptulose is found in certain plants, in particular alfalfa (Medicago sativa L), avocado, fig (Ficus officinalis L), showy stonecrop (Sedum spectabile Bor.) and primrose (Primula officinalis Jacq.). However, the highest content of D-mannoheptulose is found in avocado. D-mannoheptulose has already been used in therapeutic applications. For example, patent application WO95/03809 describes the use of D-mannoheptulose as a glucokinase inhibitor to inhibit development of tumor cells, and patent application US2003/0092669 describes an oral food supplement containing D-mannoheptulose that decreases insulin level and thus enables weight loss.

Despite the disclosures found in various scientific and medical research publications, including the above-mentioned background publications, no publication exemplifies any Hylotelephium composition as histamine receptor antagonists for preventing and treating the conditions or disorders mediated by histamine receptors. Moreover, prior to the present invention, none of prior art studies suggest these newly discovered effects of the plant Hylotelephium spectabile (Boreau) H.Ohba disclosed in the present invention.

The present invention encompasses Hylotelephium composition as histamine receptor antagonists for preventing and treating the conditions or disorders
mediated by histamine receptors. The methods and compositions described in the present invention are believed to provide the hitherto undiscovered effects of Hylotelephium composition based on the review on the known effects of Hylotelephium spectabile (Boreau) H.Ohba on mammalian health as well as hereinafter the parallel among Hylotelephium composition and histamine receptor antagonists for preventing and treating the conditions or disorders mediated by histamine receptors.

[0028] In accordance with the present invention, Hylotelephium compositions can be prepared in liquid, semi-solid, and solid forms. As used herein, the term "Hylotelephium composition" refers to a leaf extract of the plant Hylotelephium spectabile (Boreau) H.Ohba, and the term "extract" refers to liquid, semi-solid, and solid preparation.

[0029] As used herein, the term "subject" refers to a mammal, such as a human, pig, cattle, sheep, rabbit, horse, dog, cat, and rat, etc. Preferably the mammal is a human — e.g., an individual including infant, elderly, pregnant or lactating women.

[0030] The Hylotelephium composition can be administered to a subject orally, topically (e.g., eye drops, ear drops, and some forms suitable for buccal or nasal administration by inhalation, insufflations or spray of powders), or parenterally (e.g., subcutaneously, intramuscularly, intravenously, intraperitoneally, rectally, intravaginally), and the like. As discussed above, the particularly preferred route of administration is oral or topical (i.e. systemic or local).

[0031] In one aspect, the composition in a liquid form may be prepared according to the following steps. Fresh Hylotelephium leaves are washed, cleaned by rinsing with purified water, air dried at room temperature, and then frozen below -4 degree Celsius. The frozen leaves are crushed, ground into a pulp and thawed at room temperature; the thawed leaf pulp is again frozen below -4 degree Celsius, and then the frozen leaf pulp is again thawed at room temperature; the above freezing-thawing process steps are repeated as necessary in order to break cell walls and change tissue structure of the plant; the number of successive freeze-thaw
cycles ranges from zero (that is/thawing only) to six, and the particularly preferred number is three or four; the resulting leaf pulp is then separated into liquid and residual parts by appropriate methods such as filtration, or centrifugation, etc., and the liquid and the solid collected are respectively sterilized and stored at -18 degree Celsius.

[0032] A semi-solid preparation of Hylotelephium composition can be prepared from the liquid preparation further evaporated or concentrated; and the solid preparation of Hylotelephium composition can be eventually made from the semi-solid preparation or directly made from the leaves of plant Hylotelephium spectabile using standard equipment known in the art, including, but not limited to, spray drying, vacuum drying, fluid-bed drying, freeze-drying ((also known as lyophilization), and the like.

[0033] The composition according to the present invention composition can be administered in a single dose or more units of discrete products. Two or multiple doses can be administered regularly or consecutively (e.g., over a period of days or weeks). Effective amounts or doses recommended in the present invention were ascertained by trials, and it can be also ascertained by considering the following factors, for example, the mode or route of administration or drug delivery, the severity and course of conditions, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating physician, etc.

An exemplary dose is equivalent to the amount of from about 0.01 grams to about 10 grams of Hylotelephium leaves (wet weight) per kg of subject's body weight per 24 hours, preferably equivalent to the amount of from about 0.01 grams to about 6 grams of Hylotelephium leaves (wet weight) per kg of subject's body weight per 24 hours.

[0034] The dose may be adjusted to once per day for preventative or maintenance treatment once improvement of conditions or disorders has occurred, and a particularly preferred dose is equivalent to the amount of from about 0.01 grams to about 4 grams of Hylotelephium leaves (wet weight) per kg of subject's body weight per 24 hours. The subject may cease to administer if all the symptoms are relieved.
Hylotelephium Composition Further Comprising Pharmaceutically Acceptable Excipient or Carrier

According to one aspect of the present invention, the composition of the present invention includes Hylotelephium and further comprises a pharmaceutically acceptable excipient or carrier. The composition containing Hylotelephium may be mixed with pharmaceutically compatible and acceptable carriers or excipients known in the art, which include, but not limited to, diluents, medium for the active ingredient, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, sweetening agents, flavoring agents, coloring agents, preservatives as well as solid binders, suitable inert fillers (e.g., sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, and sorbitol, etc.), lubricants, and the like. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate or with an enteric coating to delay absorption in the gastrointestinal tract.

The dosage unit forms of the composition according to the present invention can be adapted to various discrete product forms of liquid, semi-solid, and solid. In one aspect, the product form depends upon the manner of packaging, intended manner of administration, and the particular indication targeted.

A liquid preparation includes, but is not limited to, solutions (e.g., sterile packaged injection, eye drops, or ear drops), suspensions, suitably flavored syrups, and emulsions with edible oils such as coconut oil and similar pharmaceutical vehicles, etc.; and the semi-solid preparation includes, but is not limited to, gel, cream, paste, and plaster, etc. Both liquid and semi-solid preparations can be used for making the topically therapeutic agents, wound dressings, cosmetics aesthetically improving appearance of the skin, the medicated shampoos to help decrease itchy scalp and dandruff, or the bioactive ingredient of functional beverages or food, and the like.

The solid preparation includes, but is not limited to, powders (e.g., sterile packaged powders for injection, nasal powder spray, buccal powder spray,
inhalation powders, insufflations powders, and topical powders, etc.), tablets, effervescent tablets, chewable tablets, rapidly disintegrating tablets, pills, capsules, polymeric microcapsules or microvesicles, dispersible granules, lozenges, suppositories. The solid preparation for rectal or vaginal administration may be suppositories that can be prepared by mixing Hylotelephium composition with suitable non-irritating carriers such as polyethylene glycol or a suppository wax, which is solid at ambient temperature but liquid at body temperature in order to melt in the rectum or vaginal cavity and release the active composition.

[0039] One aspect of the present invention includes delivering the composition in food form. For example, the composition can be added to fruit juices or beverages to produce a functional beverage as well as a dietary supplement for infants, adults, older adults, pregnant or lactating women. Similarly, the composition of the present invention can be mixed with conventional foodstuffs or made into a functional food or other delicious food enjoyed by children. All of the above will also provide more options for those children who hate taking medicines and thus can be conveniently administrated to infants or children.

[0040] The composition of the present invention can also be mixed in feed for pets, poultry, and livestock to prevent and treat the similar conditions or disorders.

**Hylotelephium Composition Further Comprising Pharmaceutical Component**

[0041] In another aspect according to the present invention, the composition may include a Hylotelephium extract and may further comprise a pharmaceutical component. The composition may be provided in a kit wherein the necessary materials are packaged into suitable containers. In one embodiment, the composition including one or more pharmaceutical components may be administered in combination with one or more additional therapeutic agents in order to reduce dosage of administered prescription drugs or provide complementary and synergistic effects for preventing and treating the said conditions or disorders.

[0042] The pharmaceutical components or additional therapeutic agents include, but are not limited to, decongestants, corticosteroids, bronchodilators, epinephrine, antihistamines (i.e. histamine receptor antagonists including H1, H2, H3,
and H4), mast cell stabilizers, leukotriene inhibitors, anticholinergics, analgesics, antipruritic agents, immunomodulators, antacids, agents for gastrointestinal ulcers, laxative, styptics, agents for promoting wound healing, as well as therapeutic agents for other conditions or disorders, for example, various dermatological disorders, respiratory tract disorders, cardiovascular and cerebrovascular disorders, non-insulin-dependent diabetes mellitus and the like.

[0043] Suitable additional therapeutic agents include decongestants and corticosteroids. In this regard, it is known that nasal congestion or stuffy nose, an allergic reaction caused by allergic rhinitis, is the blockage of the nasal passages usually due to membranes lining the nose becoming swollen resulting from inflamed blood vessels. Decongestants can provide significant symptom relief of nasal congestion. Clinically, topical decongestants are generally used to apply directly to the nasal cavity to relieve nasal congestion in order to reduce the side effects associated with systemically-acting decongestants, such as high blood pressure caused by vasoconstriction.

[0044] However, topical decongestants should only be used by patients for a maximum of three days in a row because rebound congestion may occur in the form of rhinitis medicamentosa that is a condition of rebound nasal congestion brought on by extended use of topical decongestants. Decongestants are normally paired with antihistamines to lessen this effect, but the combination of both classes of drugs does not necessarily cancel the side effects of each other. The common side effects of decongestants include sleeplessness, anxiety, dizziness, excitability, and nervousness besides hypertension.

[0045] According to the present invention, however, compositions including Hylotelephium extract can be administered in combination with topical decongestants such as phenylephrine, pseudoephedrine, and oxymetazoline, etc. For example, phenylephrine, the most common over-the-counter (OTC) decongestant in the United States, is used as a decongestant sold as an oral medicine, nasal spray, or eye drops. The composition according to the present invention may be orally administered and may be combined with topically administered phenylephrine as nasal preparation or
eye drops in the form of a kit by the different administration routes for the benefit of a reduction in the effective dosage of phenylephrine to minimize its side effects as well as relieve the symptoms of itching, conjunctival swelling, and rebound nasal congestion, etc.

[0046] Both asthma and allergic rhinitis are associated with inflammatory reactions. Inhaled corticosteroids are first-line agents for conventional treatment in severe acute asthma attacks, and they are also the first-line therapy for patients with more severe symptoms of allergic rhinitis, which are used to suppress inflammation, reduce the swelling of the lining of the airways, and treat the swollen nose membranes. Moreover, it has been reported that the availability of corticosteroid nasal sprays without prescription has increased their use by patients with allergic rhinitis, but the long-term use of corticosteroids can have many side effects.

[0047] In contrast, according to the present invention, the orally or topical administration of Hylotelephium composition in combination with inhaled corticosteroid provided in convenient kits may not only inhibit allergic inflammatory response or localized swelling but also enables patients to avoid the complications as a result of overuse of rescue medications. The synergistic effect of this combination may reduce a patient's need for the conventional treatment of topical corticosteroid to achieve a desired therapeutic outcome and thereby help to reduce the adverse effects of decongestants or corticosteroid, if necessarily administered.

[0048] According to the method of the present invention, the components of these combinations may be prepared separately into two compositions in the form of a kit for simultaneous delivery of combined components by the same or different administration routes (e.g., orally, topically, subcutaneously, intramuscularly, intravenously, intraperitoneally, rectally, or intravaginally, etc.). Moreover, each component of the combination may be administered to a subject non-simultaneously, for example, prior or after the other component is administered, or each administration may be also given non-simultaneously at several intervals over a given period of time.

[0049] The amount of pharmaceutical component included in the composition
of the present invention will be typically less than the normal amount administered in
a composition comprising the pharmaceutical component as single active agent. In
some embodiments, the amount of pharmaceutical component involved in the
preferred combination will range from about 50% to about 95% of the normal amount
administered in a composition comprising the said pharmaceutical component as
single active agent.

**Hylotelephium Composition Further Comprising Botanical Component**

According to another embodiment of the present invention, the
composition may include a Hylotelephium composition and may further comprise a
botanical component as a second active agent. In some embodiments, the
composition may be administered in combination with a botanical component as the
second active agent in order to provide complementary and synergistic effects for
preventing and treating the conditions or disorders mediated by histamine receptors.
The botanical components as the second active agent include, but are not limited to,
the juice or powder from various melon and fruit, the powder or juice of buckwheat
sprout, and the sprout juice of plants in the family Cucurbitaceae including
watermelon, cantaloupe, and honeydew melon, and the like.

Suitable botanical components include the powder or juice of
buckwheat sprout and watermelon sprout juice. The composition may include the
powder or juice of buckwheat sprout to prepare oral or topical therapeutic agents, or
with watermelon sprout juice to prepare topically therapeutic agents, for preventing
and treating the above conditions or disorders. The botanical components as the
second active agent, when present, are used in an effective amount, preferably in an
amount from about 10% to 50% of the whole composition by weight.

**Hylotelephium Composition Further Comprising the Powder or Juice of
Buckwheat Sprout**

In one suitable embodiment, the composition according to the
composition includes an extract of buckwheat sprouts. It has been shown that
extracts of buckwheat sprouts (ExtBS) contain anti-inflammatory compounds [Ishii S.,
et al, "Anti-Inflammatory Effect of Buckwheat Sprouts in Lipopolysaccharide-Activated...

[0053] Some researchers compared the differences in general composition, functional components, and antioxidant capacity between the common buckwheat sprouts (Fagopyrum esculentum Moench) and tartary buckwheat [Fagopyrum tataricum (L.) Gaertn] sprouts. The ethanol extracts of tartary buckwheat sprouts (TBS) had higher reducing power, free radical scavenging activity, and superoxide anion scavenging activity than those of common buckwheat sprouts (CBS). As for chelating effects on ferrous ions, CBS had higher values than TBS. Rutin was the major flavonoid found in these two types of buckwheat sprouts, and TBS was five-fold higher in rutin than CBS. The antioxidant effects of buckwheat sprouts on human hepatoma HepG2 cells revealed that both TBS and CBS could decrease the production of intracellular peroxide and remove the intracellular superoxide anions in HepG2 cells, but TBS reduced the cellular oxidative stress more effectively than CBS, possibly because of its higher rutin (and quercetin) content [Liu C, et al., "Antioxidant Activity of Tartary [Fagopyrum tataricum (L.) Gaertn] And Common (Fagopyrum esculentum Moench) Buckwheat Sprouts ", J Agric Food Chem. 2008 Jan 9; 56(1): 173-8].

[0054] According to another embodiment of the present invention, where the botanical component as the second active agent is combined with Hylotelephium and is the powder or juice of buckwheat sprout, the combination preparation with the powder as the second active agent is called Combination-HBP, while one with the juice as the second active agent is called Combination-HBJ for short hereinafter. In the present invention, the particularly preferred buckwheat is tartary buckwheat [Fagopyrum tataricum (L.) Gaertn].
As used herein, the term "Combination-HBP" refers to the combination preparation made from Hytotelephium composition and powder of buckwheat sprout as the second active agent; and the term "Combination-HBJ" refers to the combination preparation made from Hytotelephium composition and juice of buckwheat sprout as the second active agent.

In some embodiments, orally administering Combination-HBP may help to provide additional benefit in patients with obesity, cardiovascular and cerebrovascular disorders (e.g., arteriosclerosis, and hypertension, etc.), or non-insulin-dependent diabetes melitus, etc., who are simultaneously susceptible to or suffering from allergic and/or inflammatory conditions. Moreover, topical administration of Combination-HBJ as eye drops may be used for relief of allergic conjunctivitis, allergic rhinoconjunctivitis, or vernal keratoconjunctivitis, etc. because Combination-HBJ has the better tolerability profile than a composition containing only Hylotelephium.

**Hylotelephium Composition Further Comprising Sprout Juice of Plants in the Family Cucurbitaceae**

In the "Omnibus of Herbal Medicine in China", the muskmelon pedicle of Cucumis melo L. in the family Cucurbitaceae (commonly referred to as cucurbit including watermelon, muskmelon, cantaloupe and honeydew melon, etc.) is used to induce vomiting to discharge phlegm and fluid, retained food and toxic substances. When ground into powder or "Melon Pedicle Powder" for smelling, it is used for jaundice of damp heat. It has been suggested that Muskmelon pedicle contains cucurbitacin, which has been noted to have an anti-hepatitis effect and to prevent fatty liver. It can stimulate gastric mucous to induce vomiting. Moreover, the fruits of Cucumis melo L. can be used as a cooling light cleanser or moisturizer for the skin. They may be used as a first aid treatment for burns and abrasions.

The seeds of Cucumis melo L. (Cucurbitaceae) are used in traditional Chinese medicine as antitussive, digestive, febrifuge and vermifuge; and melon seed extract can be used as an antidiabetic and is beneficial in chronic eczema [Carmen
However, in the present invention, it has been discovered that topically applied watermelon sprout juice actually has an antipruritic and anti-hyperalgesic action. Compositions containing Hylotelephium extract may further comprise watermelon sprout juice to provide complementary, synergistic and enhancing actions for exerting the various effects of Hylotelephium composition, and the combination preparation made from Hylotelephium composition and watermelon sprout juice as the second active agent is called Combination-HW for short hereinafter.

As used herein, the term "Combination-HW" refers to the combination preparation made from Hylotelephium composition and watermelon sprout juice as the second active agent.

The topical administration of Combination-HW provides diverse bioactive properties, such as anti-inflammatory, antipruritic, analgesic, antibacterial, antimicrobial, and antifungal actions. Combination-HW may be helpful in reducing inflammation, swelling, and burning sensation; immediate relief of formication (or skin paresthesia); potent inhibition of pruritus caused by various allergic or non-allergic reactions and metabolic disorders; and elimination of inflammatory, nociceptive, or neuropathic pain. It may also be used in prevention and treatment of some conditions, including, but not limited to, angular blepharitis, angioedema, burn and scald, post trauma swelling and pain, chronic pruritus, allergic and non-allergic dermatological conditions including atopic dermatitis or eczema, hives or urticaria, insect stings, seborrheic dermatitis, sunburn, and contact dermatitis mediated by T cells, monocytes, macrophages, and the like.

In another embodiment of the present invention, Combination-HW may serve as the potential first aid treatment agent for acute partial-thickness scald or burn injuries. For instance, the topical administration of Combination-HW in a subject as needed has successfully cured the left hand scalded by just boiled water at the temperature about 203°F (i.e. 95°C), after only 20 minutes duration of...
administration, there was no trace of scalding on the previously scalded skin and the
sensation of pain after administrating the Combination-HW was reduced.

In another instance, the topical administration of Combination-HW to a
subject cured a right hand scalded by half a pot of just-cooked rice gruel at
temperature about 194°F (i.e. 90°F), and it was noticed that 20 minutes after
administration of the Combination-HW, the tiny trace as scalding did not exist on the
most scalded skins thoroughly swabbed with Combination-HW without delay. In
contrast, in those small areas where the scalded skin was not swabbed with the
Combination-HW composition, the symptoms of pain, redness, swelling and blisters
occurred.

Moreover, it is contemplated that treatment with Combination-HW
would be satisfactory if the thick gruel on the scalded skin was washed away by
running water and then the scalded area swabbed with Combination-HW.
Alternatively, it is believed that treatment with Combination-HW would be efficacious
if the scalded hand was immediately immersed in a lotion made from
Combination-HW after irrigating with running water. Moreover, after removing the
fluid within blisters, the continuous administration of Combination-HW effectively
relieved the symptoms of pain, redness and swelling of the scalded skin.

Combination-HW was also used to reduce a variety of symptoms of
rashes, wheal and flare response regarded as the cutaneous signs of histamine
release, localized swelling, burning sensation, pain and itching during the allergic or
non-allergic dermatological conditions. For example, topical administration of
Combination-HW helped a subject successfully cure angular blepharitis, which is
characterized by a range of symptoms such as redness, pain and intense itching of
canthi, i.e. corners of the eye, with some irritating discharges, and even erosion in the
skin around the canthi when it is severe. As well, Combination-HW was used to
reduce various allergic or non-allergic skin symptoms, including burning and swelling
of itchy auricles or angioedema for unknown reason; and the redness and itching
caused by seborrheic dermatitis frequently occurring around the folds of the nose and
the eyebrow areas; scar pain and the typical itching felt around a healing scab; and pain and pruritus due to insect stings; and the like.

[0066] Most scald burn injuries occur in the person's own home, usually in the kitchen or bathroom; and infants, young children, older adults and people with disabilities are the most likely to incur such injuries; and scald burns are also one the most common causes of burns in restaurants. Combination-HW may help the scald burn victims to conveniently treat the wound or the sufferers with various dermatological conditions efficiently to reduce allergic and/or inflammatory responses as early as possible at their own home or their workplace, and thereby minimize treating cost, which is exactly what consumers are demanding nowadays in the wound care and dermatology markets.

Effects of Hylotelephium Composition Compared with Histamine Receptor Antagonists

[0067] Hereinafter a comparison between compositions according to the present invention and containing Hylotelephium extract and histamine receptor antagonists is described in order to demonstrate the efficacy of compositions according to the present invention as histamine receptor antagonists for preventing and treating the conditions or disorders mediated by histamine receptors.

[0068] The various biological effects of histamine mediated through the activation of specific histamine (H1, H2, H3, and H4) receptors differ in their tissue expression patterns and functions. Histamine H1 receptor is expressed throughout the body, specifically, in smooth muscles, on vascular endothelial cells, and in the central nervous system; they cause systemic vasodilatation, smooth muscle contraction, separation of endothelial cells, itching or pain, etc. Histamine H2 receptor is located on the parietal cells and vascular smooth muscle cells; they stimulate gastric acid secretion and regulate gastrointestinal motility and intestinal secretion, and thought to be involved in regulating cell growth and differentiation. Histamine H3 receptor is found on central nervous system, peripheral nervous system tissue, and endothelial cells, etc.; they decrease such neurotransmitters as histamine release from the neurons. Histamine H4 receptor is highly expressed in
bone marrow (or on hematopoietic cells) and white blood cells, and also expressed in colon, liver, lung, small intestine, spleen, thymus, tonsils, and trachea, they have been shown to involve in chemotaxis and inflammatory mediator release by eosinophils, mast cells, monocytes, dendritic cells, and T cells. Therefore, histamine receptor antagonists (commonly known as antihistamines) to inhibit action of histamine by blocking it from attaching to four types of histamine sub-receptors (H1R, H2R, H3R and H4R) have been used in therapy for various diseases.

**Effect of Histamine Receptor Antagonists on Allergic and Inflammatory Conditions**

**[0069]** Allergy is one of four forms of hypersensitivity and is called type I (or immediate) hypersensitivity allergic reactions. It is characterized by excessive activation of mast cells and basophils by the allergen binding to the IgE antibodies held on the surface of the mast cells or basophils. Mast cells and basophils will degranulate if sensitized by IgE antibodies attached to the membranes when exposed to the environmental appropriate antigen. Activated mast cells and basophils release histamine and other chemical mediators into the surrounding tissue during the degranulation. These mediators have an effect on nerve cells causing itching, smooth muscle cells causing contraction, goblet cells causing excessive mucus production, and endothelial cells causing vasodilatation and edema.

**[0070]** For example, histamine dilates post capillary venules, activates the endothelium, and increases blood vessel permeability. This leads to local edema (swelling), warmth, redness, and the attraction of other inflammatory cells to the site of histamine release. Histamine also irritates nerve endings leading to itching or pain by acting on sensory nerve terminals. Clinically, histamine H1 receptor antagonists (or H1 antihistamines) are commonly used on a regular basis, rather than as needed, to reduce effects mediated by histamine as an endogenous chemical mediator released during allergic responses and thereby to suppress various symptoms caused by allergies and inflammation.

**[0071]** Allergic rhinitis (i.e. hay fever or pollenosis) is a common disease marked by rhinorrhea, nasal congestion, nasal itching, and sneezing. Oral H1
antihistamines are first-line therapy for mild-to-moderate allergic rhinitis. Some of
the newer oral antihistamines, such as cetirizine, desloratadine, and fexofenadine,
have been shown to relieve the symptom of nasal congestion [Rosenwasser LJ.
"Treatment of allergic rhinitis" Am J Med. 2002 Dec 16; 113 Suppl 9A: 17S-24S (See:

Histamine H3 receptors play a role in the regulation and release of
several neurotransmitters. Receptor activation by histamine results in the inhibition
of neurotransmitter release, although many of the symptoms of allergic rhinitis can be
treated by histamine H1 antagonists, nasal congestion persists. In the nasal
mucosa, activation of H3 receptors by histamine results in a reduction of
norepinephrine outflow which contributes to nasal congestion. It has been shown
that histamine H3 antagonists may reverse the effects of nasal blockage elicited by
histamine release [Nicholas i. Carruthers, "Translational approaches towards the
identification of a histamine H3 receptor antagonist and its' clinical evaluation for the
symptomatic treatment of allergic rhinitis" European Histamine research Society 39th
meeting Durham, UK 13th-16th July 2010 (See:

Asthma is a complex inflammatory airway disease characterized by the
presence of cells such as eosinophils, mast cells, basophils, and T lymphocytes in the
airway walls, and this airway inflammation causes recurrent episodes of wheezing,
breathlessness, coughing, chest tightness, and excessive mucus secretion. Some
people with asthma only rarely experience symptoms, usually in response to triggers,
whereas other may have marked persistent airflow obstruction. The inflammatory
responses caused by histamine have long been thought to be mediated by histamine
H1 receptors, and histamine H1 receptor antagonists have been used to treat allergic
and inflammatory conditions for many years. However, H1 receptor antagonists
have been found only partially effective in relieving symptoms caused by asthma and
atopic allergies though they offer symptomatic relief in atopic nasal, conjunctival and
skin disease.

In the last years, researchers have investigated the roles of histamine
H1, H2, H3, and H4 receptors in acute itch induced by histamine [Bell JK, et al., "Involvement of histamine H4 and H1 receptors in scratching induced by histamine receptor agonists in Balb C mice" Br J Pharmacol. 2004 May; 142(2): 374-80. Epub 2004 Apr 5 (or see: http://www.ncbi.nlm.nih.gov/pubmed/1 5066908)]. It has been discovered that H4R is involved in chemotaxis and inflammatory mediator release by eosinophils, mast cells, monocytes, dendritic cells, and T cells and that H4R antagonists have shown promise in experimental models of asthma and pruritus, two conditions where currently marketed antihistamines targeting histamine H1 receptor are not optimally effective in humans. It has also been suggested that a new class of H4R-specific antihistamines may be distinctively effective in treating allergic diseases associated with chronic pruritus and asthma [Huang JF, et al., "The new biology of histamine receptors" Curr Allergy Asthma Rep. 2008 Mar; 8(1): 21-7. (See: http://www.ncbi.nlm.nih.gov/pubmed/1 83777707itooNEntrezSystem2.PEntrez. Pubmed_Pubmed_ResultsPanel.Pubmed_RVDocSum&ordinalpos=2)].

[0075] It has been reported that using histamine H1, H2, H3, and H4 receptor antagonists to treat and prevent asthma and allergic inflammatory conditions. For example, United States Patent Application 2004/0127395 describes the effects of histamine H4 receptor modulators on asthma and/or allergic responses. Also, United States Patent Application 2005/0090527 describes a method for treating or preventing an allergic or non-allergic condition with characteristics of airway inflammation. It has been suggested that some combinations of various histamine receptor antagonists can be used for treating pruritus. For example, United States Patent Application 2009/0069343 describes a method of treating a subject suffering from pruritus by administering at least one histamine H1 receptor antagonist with centrally acting and at least one histamine H4 receptor antagonist to such subject.

[0076] Allergic conjunctivitis is inflammation of the conjunctiva due to allergy, and the most common cause is hay fever. Symptoms consist of redness due to vasodilation of the peripheral small blood vessels, edema of the conjunctiva, itching and increased lacrimation (production of tears). Moreover, allergic rhinoconjunctivitis may occur if allergic conjunctivitis is combined with rhinitis. One
treatment of allergic conjunctivitis is to avoid the allergen and to use antihistamines, either topical (in the form of eye drops) or systemic (in the form of tablets) to stabilize mast cells (http://en.wikipedia.org/wiki/Allergic_conjunctivitis).


[0079] Food allergies are thought to develop more easily in patients with an atopic syndrome, which is a very common combination of diseases including allergic rhinitis, allergic conjunctivitis, eczema, and asthma. The symptoms of IgE antibodies mediated food allergies include hives (or urticaria) appearing as red and itchy bumps; eczema triggered by an irritant (or mainly caused by food allergies), a
dry and bumpy rash, also known as atopic dermatitis; and some other symptoms affecting the skin, gastrointestinal tract, respiratory tract and blood circulation. The mainstay of treatment for food allergies is avoidance of the foods that have been identified as allergens, and the treatments include antihistamines, and steroids, etc. (http://en.wikipedia.org/wiki/Food_allergy).

In brief, use of histamine receptor antagonists is an established approach to block histamine effects on allergic and inflammatory conditions based on histamine has been recognized as a key factor in the pathogenesis of allergic and inflammatory conditions.

Effect of Hylotelephium Composition on Allergic and Inflammatory Conditions

The various evidence accumulated in conducted trials indicate that compositions according to the present invention and including Hylotelephium extracts have diverse bioactive properties and the effects most similar to that of histamine receptor antagonists in preventing and treating allergic and inflammatory conditions. Hereinafter, the preferred embodiments and concrete examples herein will reveal the efficacy of Hylotelephium composition as histamine receptor antagonists for preventing and treating the conditions. The following Examples are given for the purpose of illustration only and are not intended to limit the scope of the present invention.

One aspect of the present invention provides a method of treating certain allergic and/or inflammatory conditions by administering a composition containing a Hylotelephium extract where allergic and/or inflammatory conditions include, but are not limited to, allergic asthma, non-allergic asthma and airway inflammation, exercise-induced asthma, bronchitis, allergic rhinitis (sometime referred to as "hay fever" also called pollinosis) including seasonal and perennial allergic rhinitis, non-allergic rhinitis, nasal congestion, allergic sinusitis, rhinitis medicamentosa, allergic rhinoconjunctivitis, allergic conjunctivitis, angular blepharitis, otitis media, headaches, colds, food allergies, atopic dermatitis/eczema, insect sting allergy, atopic syndrome, inflammatory or neuropathic pain, chronic pruritus, angioedema on the skin, actinic dermatitis, contact dermatitis caused by the unknown
irritants in allergic or non-allergic reactions, hives (or urticarial), fixed drug eruption, urticaria pigmentosa, mastocytosis, cystic fibrosis, pulmonary fibrosis, systemic sclerosis, psoriasis, respiratory disorders associated with excess airway mucus production, chronic obstructive lung disease (COPD), emphysema, gastrointestinal tract diseases, intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), scalds and burns, wound healing, inflammation response caused by ionizing radiation, and the like.

[0083] Particular conditions treated, ameliorated, or reduced by administration of compositions according to the present invention include allergic asthma, allergic rhinitis, allergic conjunctivitis, angular blepharitis, allergic rhinoconjunctivitis, nasal congestion, allergic sinusitis, rhinitis medicamentosa, food allergies, atopic dermatitis/eczema, hives (or urticarial), atopic syndrome, insect sting allergy, angioedema, inflammatory or neuropathic pain, chronic pruritus, scalds and burns, wound healing, inflammatory response caused by ionizing radiation.

[0084] In suitable embodiments, the composition according to the present invention can be administered either orally or topically (through the skin, nose, or eyes), or both. Alternatively, according to the present invention one method includes administering an effective amount of a composition containing an effective amount of a Hylotelephium extract, or the different combination preparations described above, including Combination-HBP, Combination-HBJ, and Combination-HW, may help a subject to significantly reduce the risk of allergic and inflammation responses.

**Asthma, Allergic Rhinitis, and Allergic Conjunctivitis**

[0085] Asthma is airway inflammation with reversible airflow obstruction, bronchospasm, and variable and recurring symptoms include wheezing, coughing, chest tightness, and shortness of breath. The release of histamine and mast cell degranulation play a crucial role in the pathogenesis of immediate allergic reaction and cause goblet cell hyperplasia resulting in excessive mucus production and secretion, while goblet cell hyperplasia is a prominent feature of chronic allergic
airway inflammation such as asthma. Moreover, therapeutic H4R antagonism inhibited T cell infiltration into the lung and decreased Th2 cytokines IL-13 and IL-5. IL-13 dependent remodeling parameters such as goblet cell hyperplasia (GCH) and lung collagen were reduced. [Cowden JM, et al, "Histamine H4 receptor antagonism diminishes existing airway inflammation and dysfunction via modulation of Th2 cytokines" Respir Res. 2010 Jun 24; 11:86 (or see: http://www.ncbi.nlm.nih.gov/pubmed/20573261)].

[0086] In the present invention, orally administering an effective amount of Hylotelephium composition, only when needed, successfully cured a subject's acute asthma attacks following exposure to the odors of insecticide dichlorvos or cooking odors of frying chili pepper, etc. Although acute asthma attacks always occurred whenever the subject was exposed to the appropriate allergens or irritants from air pollutants, when a composition according to the present invention and containing an Hylotelephium extract was orally administered the symptoms of asthma, whenever occurred, were immediately relieved, including chest pain or tightness, shortness of breath, wheezing, cough, and frequent expectorating phlegm. More particularly, the inordinate production and secretion of mucus was successfully eliminated, even within several minutes, which demonstrated that the composition containing Hylotelephium extract possibly suppressed goblet cell hyperplasia and thereby reduced excessive production and secretion of mucus from the airways.

[0087] Allergens can bind to IgE-loaded mast cells in the nasal mucosa, it leads to three clinical responses: sneezing due to histamine-associated sensory neural stimulation; hypersecretion from glandular tissue occurs; nasal mucosal congestion due to vascular engorgement associated with vasodilation and increased capillary permeability [Monroe EW, et al., "Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines" J Allergy Clin Immunol. 1997 Feb;99(2):S798-806 (or see: http://www.ncbi.nlm.nih.gov/pubmed/9042073)]. In addition, the study speculated that the H4 receptor mediated histamine effects have a role in eosinophil accumulation and activation in inflammatory diseases of the nasal and paranasal

[0088] In the present invention, the composition containing Hylotelephium extract may help to subject to alleviate (when used before exposure to allergic triggers) or treat (only when needed) allergic rhinitis without the need to combine with a decongestant; while histamine H1 antagonists, in addition to needing to combine with a decongestant, are best taken on a regular basis rather than as needed. For example, orally administering an effective amount of a composition containing Hylotelephium extract to a subject as needed helped to reduce the symptom of runny nose or stuffy nose (i.e. nasal congestion), sneezing, itchy sensation in the eyes, nose, throat, or palate, and sometimes headache. Moreover, the composition containing Hylotelephium extract was often also used for preventing the progression of allergic rhinitis to asthma.

[0089] The efficacy of Hylotelephium extract seems to be closely related to blockade of H1-receptors on nasal sensory nerves, relief of vascular engorgement associated with vasodilation and increased capillary permeability, and inhibition of abnormal proliferation of goblet cells.

[0090] Allergic conjunctivitis resulting from an allergic reaction of the body's immune system to an allergen is common in people who have other signs of allergic disease such as hay fever, asthma and eczema. Either compositions containing Hylotelephium extract or Combination-HBJ as eye drops helped to prevent and reduce symptoms caused by allergic conjunctivitis, allergic rhinoconjunctivitis, or vernal keratoconjunctivitis, such as: ocular redness and swelling of the conjunctiva as a result of dilation of the peripheral small blood vessels; severely itchy and watery eyes with foreign body sensation caused by nerve endings irritated and increase secretion of tears in consequence of histamine release; and the like.

Allergic and Non-allergic Dermatological Conditions

[0091] Histamine and other pro-inflammatory substances are released from
mast cells, basophils and other inflammatory cells in response to the binding of allergen-bound IgE antibodies to histamine receptors. Therefore, histamine is thought to play an important role, especially in a variety of skin inflammatory conditions such as ionizing radiation, eczema, hives (or urticarial), insect stings, and contact dermatitis caused by the unknown irritants in allergic or non-allergic reactions.


[0093] The study suggests that radiation-induced mast cell mediators have a tremendous impact on inflammatory cell recruitment into irradiated skin, and it is postulated that activation of mast cells to be an initial key event in the cutaneous radiation reaction, which might offer promising targets for treatment of both the side effects in radiation therapy and radiation injuries [Miiller K, et al., "Radiation-induced mast cell mediators differentially modulate chemokine release from dermal fibroblasts" J Dermatol Sci. 2011 Mar; 61(3): 199-205. Epub 2011 Jan 15 (or see: http://www.ncbi.nlm.nih.gov/pubmed/21292447)].

[0094] In one embodiment, Hylotelephium extract seemed to prevent and reduce the inflammatory response in tissues and organs of the body damaged by ultraviolet light or ionizing radiation in radiation therapy, and it was used to treat sunburns or skin inflammation caused by overexposure to direct sunlight to reduce the symptoms of redness, itching, pain, even blistering. For example, after Trial 1, the erythema or red spots on a subject's face decreased in size almost a half as well
as the rest part distinctly faded rather than growing progressively and developing into a brown spot (i.e. age spot) like previously.

[0095] According to Dr. Duke's Phytochemical and Ethnobotanical Databases (See: http://www.ars-grin.gov/cgi-bin/duke/ethnobot.pl?Sedum%20spectabile), Hylotelephium spectabile or Sedum spectabile has sialogogue effect to stimulate the secretion of saliva. Therefore, Hylotelephium composition orally administered or dissolved in artificial saliva and administered in a mouth spray may hold promise in relief of xerostomia (i.e. oral dryness) symptom in patients with Sjogren's syndrome or patients undergoing radiation therapy to the head and neck region as well as reducing the inflammatory response and protecting the irradiated tissues against ionizing radiation damage.

[0096] Eczema with itchy rashes, localized swelling of the skin, and inflammation of the epidermis is also known as atopic dermatitis, and is triggered by an irritant or may result from food allergies and is thought to be able to lead to other allergic conditions. In one embodiment of the present invention, when topically administrating Hylotelephium composition to a subject with eczema because of eating certain shellfish products, etc., all the symptoms of skin inflammation such as recurring bumpy rashes, swelling, and pruritus were well controlled during a flare up of eczema. In another embodiment, the topical administration of Hylotelephium extract composition successfully helped a 16 year old boy cure eczema on his scrotum and the symptoms of intense itching, redness, and many papules were effectively relieved after only about 3-4 days with no later reoccurrence.

[0097] Hives (or urticarial), a kind of red puffy rashes of itchy skin with irritation and burning sensation, is frequently caused by allergic or non-allergic reactions. Most cases of hives are allergic hives caused by allergens such as medications, cosmetic products, foods, or any other environment substance by which a subject's immune system can become negatively affected. In the present invention, either oral or topical, or both, administration of Hylotelephium extract compositions to a subject as well as topical administration of Combination-HW helped to control the symptoms in hives. For example, it successfully relieved such allergic inflammatory reactions as
redness, pruritus, wheal or rashes, and swelling or inflammation within the skin caused by getting in touch with irritants (e.g. the peel of Chinese yam, or rhizoma dioscoreae), cosmetics (some sensitive skin moisturizers), medicines (e.g. sulfanilamide, etc.), or certain unknown irritants from the environment.

[0098] In addition to inhibition of pruritus, the clinical and animal data suggest that antihistamines may have efficacy in the management of pain. It has been suggested that diphenhydramine may be useful in the treatment of neuropathic and nociceptive pain that has failed to respond to treatment with opioids and adjuvant analgesics [Santiago-Palma J, et al., "Diphenhydramine as an analgesic adjuvant in refractory cancer pain" J Pain Symptom Manage 2001 Aug; 22(2): 699-703 (or see: http://www.ncbi.nlm.nih.gov/pubmed/1 1495716)].

[0099] Other suitable embodiments according to the present invention include administering Hylotelephium extract compositions to block histamine H1 receptor on peripheral nociceptors or pain-sensitive nerve endings, and consequently, to reduce sensitivity to nociceptive stimulus in inflammatory, nociceptive, or neuropathic pain. For example, when a small piece of skin on the hand of a subject was scraped away by the edge of a metal object, topical administration of Hylotelephium composition made the wound immediately stop bleeding, reduced pain and post trauma swelling, and healed within 3-4 days only leaving a blurred spot on the injured site.

[00100] For some people with insect sting allergy, the sites stung by an insect develop redness, swelling and itching. This means that their immune systems overreact to the venom of stinging insects. Their body produces IgE antibodies after the first sting; if stung again by the same kind of insect, the venom interacts with this specific IgE antibody, triggering the release of substances that cause an allergic reaction (http://www.aaaai.org/patients/publicedmat/tips/stinginginsect.stm). The swelling, if allergic, can be helped by the provision of an anti-histamine ointment (http://en.wikipedia.org/wiki/Insect_sting_allergy).

[00101] In one aspect of the present invention, topical administration of a Hylotelephium extract composition or Combination-HW satisfactorily suppressed the symptoms of redness, swelling, pain, itching, wheal or rashes immediately occurring
following mosquito bites and insect stings.

**Atopic Syndrome**

[00102] Atopic syndrome (or atopy) is a disease with one or more of the presenting conditions: allergic asthma, allergic rhinitis (i.e. hay fever or pollinosis), allergic conjunctivitis, eczema (atopic dermatitis), or hives (or urticarial); and a subject with atopic syndrome often has a tendency to have food allergies. In a further embodiment, simultaneously or non-simultaneously oral administration of Hylotelephium extract composition or Combination-HBP as well as topical administration of Hylotelephium extract composition, Combination-HBJ, or Combination-HW to the subject with atopic syndrome helped to minimize a mixture of symptoms resulting from different allergic conditions at the same time after the body is exposed to the appropriate allergen or irritants from air pollutants or food.

[00103] Moreover, Hylotelephium extract compositions can be conveniently administered to a subject based on specific symptom occurrences. For example, when allergic rhinoconjunctivitis (i.e. allergic conjunctivitis occurred in conjunction with allergic rhinitis) occurred, administration of the eye drops to relieve the symptoms of allergic conjunctivitis and oral administration to eliminate the various symptoms of allergic rhinitis was found to be effective. At the same time, use of a Hylotelephium extract composition or Combination-HW to eliminate the symptoms of irritation, redness, pain, itching, or localized swelling on the skin due to allergic and non-allergic skin reactions. The above administration method of the Hylotelephium extract composition according to the present invention enabled a sufferer to efficiently and conveniently to treat a mixture of symptoms as quickly as possible, even within several minutes, in accordance with the specific needs.

**Food Allergies and Gastrointestinal Conditions**

[00104] Food allergies, particularly IgE mediated food allergies are classified as type-I immediate hypersensitivity, and the symptoms affect the skin, gastrointestinal tract, and in severe cases, the respiratory tract and blood circulation. It is thought that food allergens trigger an inflammatory response involving mast cell degranulation and recruitment of eosinophils.
In an embodiment according to the present invention, either Hylotelephium composition or Combination-HBP helped a subject to reduce allergic symptoms caused by food. For example, oral administration of either Hylotelephium extract composition or Combination-HBP in the subject greatly reduced the risks of asthma attacks induced by pungent, more salty food, and certain food with the appropriate allergens; inhibited stomachache after eating crabmeat or cold food, etc.; and relieved stomach cramps resulting from eating dried small shrimps. In addition to relief of food allergic symptoms caused by intolerances of proteins and indigestion, it strongly inhibited excessive gastric acid secretion due to eating soy beans, red beans, bean products, leek, potato, sweet potato, and various foods high in histamine content. Fortunately, the Hylotelephium extract composition or Combination-HBP compositions according to the present invention allowed the subject to eat all of the above foods without unduly suffering from the effects of the allergies.

The results indicate that both Hylotelephium composition and Combination-HBP may have the actions similar to that of histamine H2 receptor antagonist used in the treatment of acid-related gastrointestinal conditions, including peptic ulcer disease, gastroesophageal reflux disease, and dyspepsia, etc. Consequently, each may be useful for inhibiting the production of gastric acid, reducing the secretion of gastric acid, and relieving the symptoms of acid indigestion, heartburn, stomachache, stomach cramps, and abdominal pain, etc. Therefore, they may hold promise in prevention and treatment of peptic ulcers and gastrointestinal tract diseases such as intestinal inflammatory diseases secondary to radiation exposure or allergen exposure, inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis), and the like.

Autoimmune Disorders or Conditions

Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body, or the body actually attacks its own cells due to the immune system mistakes some part of the body as a pathogen and attacks it. Common autoimmune diseases include rheumatoid arthritis, alopecia areata, bullous pemphigoid, multiple sclerosis,
Hashimoto's thyroiditis, diabetes mellitus type 1, and lupus erythematosus, etc. (http://en.wikipedia.org/wiki/Immune_system). The treatment of autoimmune diseases is typically with immunosuppression to decrease the immune response (http://en.wikipedia.org/wiki/Autoimmune_disease).

[00108] Histamine and the cells that produce it, such as mast cells and basophils, have long been thought to be involved in allergic conditions, but there has recently been recognition that they may also play a role in various autoimmune diseases. On the basis of the fact that the H4R has function in mast cells, basophils, dendritic cells and T cells, antagonists for the receptor may be useful in treating autoimmune diseases in addition to allergy [Zhang M., et al., “The histamine H4 receptor in autoimmune disease” Expert Opin Investig Drugs. 2006 Nov; 15(11):1443-52 (or see: http://www.ncbi.nlm.nih.gov/pubmed/17040202)].

[00109] Mast cells are implicated in the pathology associated with autoimmune disorders such as rheumatoid arthritis, bullous pemphigoid, and multiple sclerosis. They have been shown to be involved in the recruitment of inflammatory cells to the joints (e.g. rheumatoid arthritis) and skin (e.g. bullous pemphigoid) and this activity is dependent on antibodies and complement components (http://en.wikipedia.org/wiki/Mast_cell).

[00110] In the present invention, Trial I revealed that a Hylotelephium extract composition according to the present invention seemed to be useful in suppressing overactive immune response associated with autoimmune conditions. In some instances, autoimmune disorders include, but are not limited to, rheumatoid arthritis, osteoarthritis, alopecia areata, bullous pemphigoid, scleroderma, and the like. Particular targeted disorders are rheumatoid arthritis, osteoarthritis, and alopecia areata.

**Rheumatoid Arthritis and Osteoarthritis**

[00111] Rheumatoid arthritis is considered a systemic autoimmune disease because autoimmunity plays a pivotal role in both its chronicity and progression, but principally attacks synovial joints in addition to affecting many tissues and organs (http://en.wikipedia.org/wiki/Rheumatoid_arthritis). Histamine has been recognized
to play a role in rheumatoid arthritis that is characterized mainly by synovial tissue inflammation leading to erosion and destruction of articular cartilage with subsequent joint deformity (Woolley DE, et al., "Observations on the microenvironmental nature of cartilage degradation in rheumatoid arthritis" Ann Rheum Dis. 1997 Mar; 56(3): 151-61). Moreover, the localization of H4 receptors in synovial and vascular wall cells of patients with rheumatoid arthritis and osteoarthritis further support the contribution of the receptor in the pathophysiology of the disease (Grzybowska-Kowalczyk A, et al., "Distribution pattern of histamine H4 receptor in human synovial tissue from patients with rheumatoid arthritis" Inflamm Res. 2007 Apr; 56 Suppl 1:S59-60; and "Expression of histamine H4 receptor in human osteoarthritic synovial tissue" Inflamm Res. 2008; 57 Suppl 1:S63-4).


[00113] In one example, a subject once suffered juvenile rheumatoid arthritis in childhood, experienced one acute attack of severe rheumatoid arthritis and was in the hospital for treatment for two months at the age of 27, thus the finger joints and toe joints have become somewhat deformed, especially the joints of the little fingers. However, by Trial 1, the administration of Hylotelephium composition helped the subject to relieve symptoms of swollen, painful and stiff in the joints of the fingers particularly early in the morning and also reduce symptoms of pain and discomfort sensation in the synovial joints of the knees when ascending or descending stairs. Concurrently, it greatly reduced the attacks of the abrupt joint contracture in the little fingers frequently recurring before Trial 1.

[00114] In another example, notwithstanding the subject's left wrist often suddenly produced idiopathic pain for unknown reasons, and it was so painful that the left hand could not hold anything, the oral administration of Hylotelephium composition as needed efficaciously inhibited the pain and rapidly recovered all
functions of the left hand. Consequently, it was believed that Hylotelephium extract composition may potentially work for preventing future destruction of the joints, slowing the disease progression as well as improving joint mobility by controlling inflammation, relieving pain, and suppressing the overactive immune response. So it minimized the usage of the medicaments in prevention and treatment of rheumatoid arthritis or osteoarthritis.

Alopecia and Alopecia Areata

[00115] Alopecia areata is thought to be an autoimmune disorder in which the body attacks its own hair follicles and suppresses or stops hair growth. There is evidence that T cell lymphocytes cluster around these follicles, causing inflammation and subsequent hair loss. An unknown environmental trigger such as emotional stress or a pathogen is thought to combine with hereditary factors to cause the condition. Oral corticosteroids decrease the hair loss, but only for the period during which they are taken, and these drugs have adverse side effects. Additionally, Diphenylcyclopropenone has shown a significant hair re-growth in 40% of patients with alopecia areata at 6 months, being sustained in two thirds of these after a 12-month-follow up-period (http://en.wikipedia.org/wiki/Alopecia_areata).

[00116] According to the suggestion, histamine is also related to the induction of hair loss by continual inflammation follicles can stop producing hair. This can also result from inner stress and tension occurring direct or indirectly from a high level of histamine (http://histamino.wordpress.com/category/histamine-intolerance/symptoms-of-histamine-intolerance/).

[00117] In one example, the head of a subject was bumped which led to excess bleeding, and was treated by suturing in an emergency department because of an accident in the year before Trial I. The result is a scar more than 1*1 cm in size left in the top of the head, however, it was unexpectedly discovered that the scar has completely disappeared, and the hair has been healthily growing on the area bumped and sutured though Trial I had been terminated 3 months ago. Furthermore, the subject was also often bothered by many hair lost in the shower before Trial I.
however, the problem of hair loss no longer happened after Trial I.

[00118] It was indicated that a Hylotelephium extract composition may be helpful for reducing excessive hair loss and stimulating hair re-growth through its anti-inflammatory and immunosuppressive actions already proven in other embodiments mentioned in the present invention. Consequently, it is hypothesized that a Hylotelephium extract composition may be useful in prevention and treatment of alopecia areata and alopecia that occurs with chemotherapy or alopecia caused by other certain reasons.

[00119] Based on the above results, it is hypothesized that a Hylotelephium extract composition may be sufficient to improve the allergic constitution of the subject susceptible to various allergic reactions and the quality of life.

Conditions Associated with Abnormal Cell Proliferation

[00120] Conditions associated with abnormal cell proliferation include, but are not limited to, the abnormal proliferation of goblet cells, fibroblasts, melanocytes, keratinocytes, benign or malignant tumor cells. Particular conditions or disorders include the abnormal proliferation of goblet cells, fibroblasts, melanocytes, keratinocytes, and benign tumor cells.

[00121] In the present invention, in addition to potently suppressing the abnormal proliferation of goblet cells (or goblet cell hyperplasia) in allergic airway inflammation by orally administering Hylotelephium composition only when needed, Hylotelephium extract composition seemed to have the ability to control the abnormal proliferation of fibroblasts, melanocytes, keratinocytes, and benign tumor cells. For example, although Trial I had been terminated, compared to the baseline, the skin appearance of a subject was improved, and the substantial changes continued even several months after Trial I. The outcome of these actions adequately demonstrated that Hylotelephium extract composition may possess noteworthy actions in prevention and treatment of the conditions associated with abnormal cell proliferation.

[00122] Certain other preferred embodiments and herein will reveal the efficacy of Hylotelephium extract composition for suppressing abnormal proliferation of the above-mentioned cells. The following Examples are given for the purpose of
illustration only and are not intended to limit the scope of the present invention.

**Proliferation of Fibroblasts**

[00123] According to some investigations, mediated by the release of soluble mediators such as histamine, etc., mast cells have been shown to promote fibroblast proliferation. Increased numbers of mast cells have been reported during the active period of hypertrophic and keloid scar formation ["Hypertrophic Scarring and Keloids: Pathomechanisms and Current and Emerging Treatment Strategies" Mol Med. 2011 Jan-Feb; 17(1-2): 113-125 (or see: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3022978/)].

[00124] The fibroblast proliferation and deposition of extracellular matrix (or ECM, with collagen as a major ECM molecule synthesized in fibrotic lesions) may result in scar formation or fibrosis after injury or medical intervention in the affected tissues. On the other hand, the scarring is created by fibroblast proliferation, or a scar in tissue and organ of the body is the evidence of fibrosis in a reparative or reactive process. For example the various type scars resulting from hyperproliferation of the connective tissue of the skin in wound healing: radiation-induced lung injury, most commonly occurring as a result of radiation therapy administered to treat cancer, involving in early inflammatory damage (radiation pneumonitis) and later complications of chronically scarring (radiation fibrosis); cirrhosis characterized by replacement of liver tissue by fibrosis or scar tissue and regenerative nodules; Dupuytren's contracture with thickening and shortening of palmar fascia that leads to flexion deformities of the fingers caused by fibroblastic proliferation and disorderly collagen deposition; scleroderma with excess collagen made by fibroblasts in the skin or other tissue and organs; and the like. All of the said conditions can lead to the destruction of architecture and function of normal tissue and organ.

[00125] According to an example described above where the head of a subject was bumped and sutured in an emergency department because of an accident in the year before Trial 1, and the result was a scar more than 1*1 cm in size left in the top of the head. It was unexpectedly discovered that the scar has
completely disappeared, and the hair have been healthily growing on the area bumped and sutured though Trial I had been terminated 3 months ago.

[00126] Excitingly, no matter how old the scar, Hyiotelephium extract composition could successfully function in treatment of old scars in addition to effectually reducing formation of scar tissue (or fibrosis) and working on new scars after skin injury. For instance, in the skin of a subject, old excessive scars were left by improper suturing during a cesarean section 22 years ago. At that time, the scars were further worsened by the scar inflammation diet (e.g. red meat and shellfish to increase arachidonic acid leading to raised inflammation levels), and it made the scars already developed into one hypertrophic scar at the site of the vertical incision and twenty suture mark scars like rolling scars (or spoon-shaped scars). It is encouraging that the old scars were gradually broken-down after Trial I, such as, the hypertrophic scar was progressively softening, flattening out, and fading; the sunken recesses of suture mark scars like rolling scars appeared partially already lifted, and then suture mark scars have been also partly smoothed out when compared to the baseline. Moreover, the scars on the left hand of the subject resulting from the resection of the angioma in the dermis in 2000 with the three suturing scar marks have partially disappeared.

[00127] The above-mentioned examples indicate that Hyiotelephium extract compositions seemed potently to suppress the proliferation of fibroblasts and reduce disorderly collagen deposition so that scar formation was limited. Concurrently, the results in treatment of both new and old scars showed that Hyiotelephium extract compositions seemed to promote the new cells to grow, while old abnormal cells were possibly replaced by them, simultaneously exert action on degradation of disorderly extracellular matrix already deposited at a scar site, thus both new and old scars were progressively broken-down after Trial I. Therefore, Hyiotelephium extract composition may be used for preventing and treating various scar tissues, including hypertrophic scars, keloid scars, atrophic scars, contracture scars, and stretch marks, and the like.

[00128] Consequently, in addition to scar tissue or fibrosis resulting from
hyperproliferation of the connective tissue of the skin in wound healing, Hylotelephium extract compositions may hold great promise for preventing and treating some progressive fibroproliferative diseases that can lead to the destruction of architecture and function of normal tissue and organ, such as radiation-induced lung injury, liver cirrhosis, kidney fibrosis, Dupuytren's contracture, and scleroderma, etc., where functional tissue is replaced with scar tissue after injury or medical intervention in the affected tissues. In particular, Hylotelephium extract compositions appear to be in preventing and treating radiation-induced lung injury with early inflammatory damage (radiation pneumonitis) and later complications of chronically scarring (radiation fibrosis) resulting from radiation therapy administered to treat cancer.

Proliferation of Melanocytes, Keratinocytes and Tumor Cells


[00130] Moreover, is has been postulated that histamine is involved in ultraviolet B-induced pigmentation and that famotidine suppressed the pigmentation by the prevention of histamine binding to H2 receptors in melanocytes but not by prevention of ultraviolet B permeability and inflammation [Yoshida M, et al, "Histamine is involved in ultraviolet B-induced pigmentation of guinea pig skin" J Invest Dermatol. 2002 Feb;118(2):255-60 (or see: http://www.ncbi.nlm.nih.gov/pubmed/11841541)].

[00131] The excessive accumulations of melanin produced by melanocytes or
its abnormal distribution found in the epidermis or both in the epidermis and the
dermis can lead to various hyperpigmentation conditions, such as hyperpigmentation
scars and postinflammatory hyperpigmentation caused by skin aging (e.g. age spots)
and various skin inflammatory conditions like sunburns, acne, rashes, and trauma,
etc.

[00132] In certain embodiments, Hylotelephium extract compositions improved
the skin appearance of a subject, compared to the baseline, and the substantial
changes continued during several months after Trial 1, which showed that
Hylotelephium composition may exert action in prevention and treatment of
hyperpigmentation conditions.

[00133] For example, old hyperpigmentation scars on the skin of a subject
resulting from a scald burn in childhood and new hyperpigmentation scars due to
trauma not long ago have gradually faded, and even some have disappeared after
Trial 1. Likewise, numerous age spots or senile freckles have progressively
decreased in size and faded. Also new age spots (i.e. erythema or red spots) on the
subject's face appeared to decrease in size almost by one-half as well as the rest of
the part was distinctly faded rather than continuing to grow and developing into brown
spot (i.e. age spot) like previously, without Trial 1.

[00134] Additionally, after Trial 1 one round waxy flat seborrheic keratose on the
left forearm and one rectangle-like seborrheic keratose with crusted surface on the
left leg appeared to decrease in size and fade from dark brown into light tan,
seborrheic keratose also known as senile keratose, a benign form of skin tumor
localized hyperplastic hyperpigmented lesion being the condition commonly
appearing after age 40. It is noteworthy that one new round red seborrheic keratose
almost 4 cm in diameter with soft crusted surface on the left leg actually disappeared
and only left a blurred trace on its site.

[00135] Most unexpectedly, even some of the most stubborn pigmented moles
(i.e. nevocytic nevi, the benign tumors composed of nevus cells that are derived from
melanocytes) appeared to decrease in size regardless of hereditary, innate, new
growing, or their location on the body after Trial 1. Interestingly, one flesh-colored
intradermal nevus on the right upper arm with the form of raised half-bulb inherited from the mother of the subject appeared to decrease in size by about one third and to possess the peripheral tissue fold. Likewise, a purplish-black junctional nevus on the left abdomen skin of the subject with a few nevocytic nests in the definite sites disappeared; and a new flat junctional nevus grayish blue in the skin of the subject's left thumb appeared to decrease in size almost one third by compared to the baseline.

Concurrently, after Trial 1, among two dozen red moles (also known as "cherry angiomas" or "senile angiomas") on the skin of the subject, all of them appeared to gradually flatten, some seemed to have been destroyed or decreased in duration. For instance, one red mole almost 2 mm in diameter on the right breast skin of the subject was partially destroyed and faded into flesh-color; moreover, several tiny red moles about 1 mm in diameter seemed to be destroyed and progressively disappeared.

Histamine has been demonstrated to be involved in cell proliferation, embryonic development, and tumour growth. These various biological effects are mediated through the activation of specific histamine receptors (H1, H2, H3, and H4) that differ in their tissue expression patterns and functions. Researchers from Spain reported their recent observations of the anti-tumoural effect of H1 histamine antagonists on experimental and human melanomas, and the results indicated HR1 antagonists terfenadine-treatment in vitro induced melanoma cell death by apoptosis and in vivo terfenadine treatment significantly inhibited tumour growth in murine models [Blaya B, et al, "Histamine and histamine receptor antagonists in cancer biology" Inflamm Allergy Drug Targets. 2010 Jul 1;9(3):146-57 (or see: http://www.ncbi.nlm.nih.gov/pubmed/20632959)]

In addition, the research results from Japan indicated that both endogenous and exogenous histamine have ability to stimulate growth of malignant melanoma implants via H2 receptors expressed in host cells [Tomita K, et al, "Histamine regulates growth of malignant melanoma implants via H2 receptors in mice" Inflammopharmacology. 2005; 13(1-3): 281-9 (or see:
The melanocytes begin to grow out of control, and the earliest stage of melanoma starts. Melanoma, a malignant tumor of melanocytes, is caused by frequent exposure to ultraviolet radiation present in both sun rays and emitted by artificial light sources as solariums used for tanning. The Caucasians living in sunny climates having high rates of incidence in Australia, New Zealand, North America, and northern Europe (http://en.wikipedia.org/wiki/Melanoma).

In certain embodiments according to the present invention, the potential effect of Hylotelephium extract compositions in prevention and treatment of the conditions associated with abnormal proliferation of melanocytes and benign tumor cells is established. Moreover, Hylotelephium extract compositions most possibly possesses antitumor effect and may provide an adjuvant therapy for benign and malignant tumors, such as malignant tumor melanoma, to prevent carcinogenesis in the populations at high risk of melanoma caused by ultraviolet (UV) radiation as well as preventing tumorigenesis.

In addition, dandruff can be considered aesthetically displeasing and often causes itching. It has been well established that keratinocytes play a key role in the expression and generation of immunological reactions during dandruff formation. And the pathogenesis of dandruff involves hyperproliferation of keratinocytes, resulting in deregulation of keratinization (http://en.wikipedia.org/wiki/Dandruff).

In one embodiment, Hylotelephium extract composition helped resolve the problem of itchy scalp and excessive dandruff, by which a subject was being bothered before Trial I. However, it was noticed that both itchy scalp and excessive dandruff were effectively controlled during Trial I and even 3-4 months after Trial I. It showed that Hylotelephium extract composition may work to reduce excessive dandruff and itchy scalp via suppressing abnormal proliferation of keratinocytes as well as its anti-inflammatory and antipruritic effects.

To sum up, in the present invention, all aforementioned various evidences accumulated in the trials made with Hylotelephium composition and different combination preparations thereof have demonstrated that excellent safety
and effectiveness of Hylotelephium composition as histamine receptor antagonists for preventing and treating the conditions or disorders mediated by histamine receptors. Additionally, compositions and methods offer a potential new convenient way for consumers to receive multiple healthy benefits without significant down-time or other side effects.

[00144] The foregoing detailed description and accompanying examples are merely illustrative and are not to be taken as limitations upon the scope of the invention, the various changes and modifications to the embodiments wherein chosen for purposes of illustration will readily occur to those skilled in the art. To the extent that such modifications and variations do not depart from the spirit of the invention, they are intended to be included within the scope thereof.
WHAT IS CLAIMED IS:

1. A method of preventing and treating conditions or disorders mediated by histamine receptors in a subject, comprising administering to the subject an effective amount of a composition that includes a leaf extract of a plant in genus Hylotelephium in the family Crassulaceae.

2. The method of claim 1 wherein the plant is the species Hylotelephium spectabile (Boreau) H.Ohba varieties, cultivars, hybrids, and other closely related species thereof.

3. The method according to claim 2, wherein the effective amount of the composition is equivalent to an amount of from about 0.01 grams to about 5 grams of Hylotelephium leaves (wet weight) per kg of subject's body weight per 24 hours.

4. The method according to claim 1, wherein the histamine receptor antagonists are histamine H1, H2, H3 and H4 receptor antagonists.

5. The method according to claim 1, wherein the conditions or disorders mediated by histamine receptors include at least one of allergic conditions, allergic disorders, inflammatory conditions, and inflammatory disorders.

6. The method according to claim 1, wherein the conditions or disorders mediated by histamine receptors include autoimmune conditions or disorders.

7. The method according to claim 1, wherein the conditions or disorders mediated by histamine receptors include conditions or disorders associated with abnormal cell proliferation.

8. The method of claim 1 wherein the composition further comprises a pharmaceutically acceptable excipient or carrier.
9. The method of claim 1 wherein the composition further comprises a pharmaceutical component.

10. The method of claim 1 wherein the composition further comprises a botanical component as the second active agent.

11. The method of claim 1 wherein the botanical component as the second active agent includes a powder or juice of buckwheat sprout.

12. The method of claim 10 wherein the botanical component as the second active agent is sprout juice of plants in the family Cucurbitaceae.

13. The method of claim 12 wherein said composition acts as a topically anti-inflammatory, antipruritic, or analgesic agent for skin conditions, scald and burn injury.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

INV. A61K36/41 A61P37/08 A61P29/00 A61P37/06 A61P17/04

ADD.

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, CHEM ABS Data, WPI Data, BIOSIS, COMPENDEX, EMBASE, MEDLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
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Date of the actual completion of the international search: 20 September 2011

Date of mailing of the international search report: 30/09/2011

Name and mailing address of the ISA:

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Authorized officer: Pilling, Stephen
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