Abstract: Described are topical cosmetic compositions and methods ideally suited for improving the appearance of the eyelashes or eyebrow(s) of a subject. Described is the use of a lower alkyl-substituted bicycloalkane (e.g., 6-((5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one) in combination with minoxidil and optionally catalase, hair dye, temporary hair color, P. sativum, and/or pseudocatalase for improving the appearance of eyelashes and eyebrow(s), without enhancing collagen destruction potentially caused by minoxidil.
EYEBROW AND EYELASH ENHANCING FORMULATION

RELATED APPLICATION

This application claims the benefit of the filing date of United States Provisional Patent Application Serial Number 61/978,728, filed April 11, 2014, for "EYEBROW AND EYELASH ENHANCING FORMULATION," the contents of which are incorporated herein by this reference.

TECHNICAL FIELD

The application relates to compositions for topical application generally, and more particularly to a cosmetic composition for enhancing eyelashes and eyebrows of a subject and associated methods of making and using the composition.

BACKGROUND

Thinning eyebrows are a common concern among mature women. See, e.g., Z. Draelos "Thinning eyebrows a challenging problem for mature women," Dermatology Times (July 1, 2011).

Androgenetic alopecia (AGA) is considered a common chronic dermatologic condition and it affects both men and women, usually occurring in a pattern distribution. AGA is progressive hair loss, with increasing incidence with increasing age. In Caucasians subjects who are at least 70 years old, there is a prevalence of nearly 80% of men and 42% of women who have signs of AGA. A. Blumeyer et al., Evidence-based (S3) guideline for the treatment of Androgenetic alopecia in women and men, Journal of the German Society of Dermatology, Sept. 6, 2011, at SI, the contents of which are incorporated herein by this reference.

While androgens and sensitivity to androgen metabolites is thought to be associated with balding, and specifically with AGA, the exact physiological mechanism is not known. R.M. Trueb, Molecular mechanisms of androgenic alopecia, 27 Exp. Gerontology at 981, (2002).

Though AGA affects many elderly subjects it often starts at puberty. It can have serious detrimental effects on self-esteem, perceived personal attractiveness, and may lead to depression and other psychological ailments. M. Alfonso et al., The
psychological impact of hair loss among men: a multinational European study, 21
successfully treated have reported psychological benefits with improvement in
self-esteem and feelings of attractiveness. Id. As difficult psychologically as it is
for men to lose their hair, it is even more distressing for women. T.F. Cash et al.,
Psychological effects of androgenetic alopecia on women: comparisons with
balding men and with female control subjects, 29 J. Am. Acad. Dermatol., at 568,
(1993).

Though hair loss has been shown to have a significant psychological impact
on both men and women, studies have shown that many people suffering from it
never pursue therapy. See, Alfonso et al. While still others have tried various
therapies, and remained dissatisfied with the results leading to poor compliance.
See, Blumeyer et al.

One therapy currently in use is minoxidil 5% (w/w) (e.g., ROGAINE®, from
Johnson & Johnson Corp.) applied topically once or twice daily, e.g., a swab for a
period of months.

Minoxidil is an antihypertensive vasodilator medication that reduces hair loss
and promotes hair regrowth. It is available over-the-counter for the treatment of
androgenic alopecia. It has been proven clinically effective to both prevent hair loss
and in establishing some hair re-growth in subjects suffering pattern baldness.
When used for hair growth, minoxidil has to be used regularly and indefinitely to
continue the support of existing hair follicles and to maintain any hair regrowth.

Although the daily or twice daily use of minoxidil has been reported to be
effective in thickening the eyebrows, the compound is also known to be an inhibitor
of lysyl hydroxylase, an enzyme involved in collagen production. Minoxidil, thus,
has been established to decrease collagen production in vitro. Saika et al. "Effect of
lysyl hydroxylase inhibitor, minoxidil, on ultrastructure and behavior of cultured
233(6):347-53 (June 1995), the contents of which are incorporated herein by this
reference.

Decreased collagen in the skin would also help to explain at least some of the
other side effects attributed to minoxidil, such as wrinkling of the skin. Other side
effects attributed to minoxidil include an increased occurrence of gray hair, and the occurrence of deep pores in the skin, and dark circles under the subject's eyes.

Facial wrinkling and graying of hair, while symptoms of a lesser concern to some, can be of greater concern to those utilizing the topical minoxidil treatment, particularly when she or he is utilizing the treatment on a twice daily basis.

Anti-androgens are among the therapies that have been attempted to reduce hair loss from AGA or other forms of alopecia. However, various studies have shown little to no significant improvement in comparison to placebo when using a topical antiandrogen, such as fluridil. M. Sovak et al, Fluridil, a rationally designed topical agent for androgenetic alopecia: first clinical experience, 28 Dermatol Surg, at 678, (2002), the contents of which are incorporated herein by this reference. One such study examined the use of fulvestrant (70 mg/ml twice daily), an estrogen receptor antagonist, in comparison to minoxidil 2% and placebo and found no significant difference in hair growth from placebo. J. Gassmueller et al, Topical fulvestrant solution has no effect on male and postmenopausal female androgenetic alopecia: results from two randomized, proof-of-concept studies, 158 Br. J. Dermatol, at 109, (2008), the contents of which are incorporated herein by this reference. Blumeyer et al. concluded that there is little to no evidence to support the use of oral or topical anti-androgen treatment in men and women with AGA.

Blumeyer et al., at S11. In addition, there have been no instructive studies of combination therapy with minoxidil and anti-androgens. Id.

DISCLOSURE

Described is a composition ideal for enhancing eyelash or eyebrow hair that includes minoxidil and a lower alkyl-substituted bicycloalkane, e.g., 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one, which both enhances hair growth on its own and simultaneously maintains collagen in the subject's skin. The compounds are present in such an amount in the composition that they enhance hair growth in a subject, but do not unnecessarily decrease collagen production.

In addition, the composition may include Pisum sativum sprout extract (e.g., ANAGAIN®, from Migros-Genossenschafts-Bund Corp. Switzerland).
Use of the composition comprising minoxidil and the lower alkyl-substituted bicycloalkane for enhancing eyelash or eyebrow hair (e.g., growth, thickness, color, number, etc.) is also described.

Provided herein is a composition comprising, in the composition, an amount of minoxidil sufficient to increase the growth of eyelashes and/or eyebrow(s) in a human subject; an amount of a lower alkyl-substituted bicycloalkane; and optionally an amount of *P. sativum* sprout extract sufficient to increase the growth of eyelashes and/or eyebrow(s) in the human subject while simultaneously inhibiting collagen destruction in the subject caused by the minoxidil; and a cosmetically acceptable carrier.

Such a composition may further include other active or inactive ingredient(s). In certain embodiments, the composition includes catalase in an amount sufficient to bring back the natural pigmentation of the subject’s hair, the loss of which may be induced by the minoxidil.

Similarly, in certain embodiments, the composition includes a hair dye of a desired hair dye to color the subject’s hair to a desired color.

Again similarly, in certain embodiments, rather than a hair dye, a color, rather than a dye, is included in the composition and/or formulation to mask the gray hair.

Also provided is a topical formulation for enhancing the eyelashes and/or eyebrow(s) of a subject, the topical formulation comprising one of the aforementioned compositions. Such a topical formulation will typically be selected from the group consisting of a solid, an ointment, an oil, a lotion, a cream, a gel, a foam, a mousse, an aerosol, a shampoo, a hair conditioner, and a liquid.

In certain embodiments, the topical formulation is a sustained-release formulation, particularly for once a day application or dosing.

In certain embodiments, the formulation includes percutaneous permeability enhancers to improve penetration of the composition into the dermis and dermal layers through the skin barrier represented by the epidermal stratum corneum. The permeability enhancers can either be chemical or physical.

When applied to the skin of a subject, the topical formulation reduces existing wrinkles in the skin (e.g., about the eye and/or eyelid) and/or decreases the
appearance of new wrinkles in the skin over time, as compared to an otherwise identical topical formulation lacking the lower alkyl-substituted bicycloalkane.

In the topical formulation, the lower alkyl-substituted bicycloalkane will be present in an amount between about 0.001% and about 5.000% (w/w), while the minoxidil will typically be present in an amount between about 2% and about 5% (w/w), but amounts from about 0.1% to about 20% (w/w) are also contemplated.

Also provided is an improved method of enhancing the appearance of eyelashes and/or eyebrow(s) of a subject by topically applying a composition comprising minoxidil and/or P. sativum sprout extract to the eyelash and/or eyebrow area, the improvement comprising: incorporating, into the composition, a sufficient amount of lower alkyl-substituted bicycloalkane (e.g., 6-(5-ethoxyhept-1-yl) bicyclo[3.3.0]octan-3-one) to increase hair growth of eyelashes and/or eyebrow(s) when applied topically to the subject and to reduce collagen destruction in the subject’s skin caused by the minoxidil.

The lower alkyl-substituted bicycloalkane in the composition is believed to act synergistically with the minoxidil by (1) enhancing the minoxidil’s hair growth effects, while (2) decreasing its side effects associated with collagen depletion and/or destruction. Incorporating the lower alkyl-substituted bicycloalkane also may help to reduce the total dosage of minoxidil needed to achieve the desired hair growth since, in the composition with another compound that enhances hair growth by a different mechanism of action (e.g., inhibition of 5-DHT), less minoxidil and/or lower alkyl-substituted bicycloalkane may be needed to achieve the same result. Such a method improves the appearance of the subject’s hair by increasing hair growth, and enhances the appearance of the skin by reducing existing wrinkles in the skin and/or decreasing the appearance of new wrinkles in the skin. In such a method, the composition might also include catalase and/or a hair dye to address concerns associated with the graying of hair. In such a method, the composition might also include P. sativum sprout extract, to further reduce hair loss.

Methods of making the composition and formulation are also described herein.

BRIEF DESCRIPTION OF THE DRAWINGS
FIG. 1 depicts various applicators for the formulations of the disclosure.

MODE(S) FOR CARRYING OUT THE INVENTION

The term "topical," as used herein, means application onto the surface of the skin of a mammalian subject (e.g., a human subject).

The term "dermatologically-acceptable," as used herein, means that the composition or components thereof are suitable for use in contact with human skin without undue toxicity, incompatibility, instability, allergic response, and so on.

The term "cosmetically acceptable," as used herein, means that it is approved or approvable by a regulatory agency of, e.g., the U.S. or other national government or a state or local government as a cosmetic for use in humans. The term "cosmetically acceptable carrier," as used herein, refers to an approved or approvable diluent, adjuvant, excipient or carrier, such as, but not limited to, a liposome, with which a compound is incorporated or administered.

The term "therapeutically effective amount," as used herein, refers to the amount of a compound or composition that, when administered to a subject for treating a condition is sufficient to affect such treatment for the condition. The "therapeutically effective amount" will vary depending on the compound or composition, the condition and its severity and the age and weight of the subject to be treated.

The term "about," as used herein, refers to an amount within 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, and/or 1% of a disclosed or claimed quantity.

The term "androgen" or "androgen receptor," as used herein, refers to the intracellular protein receptor that specifically binds androgens, testosterone and DHT.

The term "extended release" or "sustained release," as used herein, means a dosage form that provides for the delayed, slowed over a period of time, continuous, discontinuous, or sustained release of a compound or composition.

The term "aging skin" includes, but is not limited to, all outward visible and tactilely perceptible manifestations, as well as any other macro or micro effects due to skin aging. Such signs may be induced or caused by extrinsic factors or intrinsic
factors, e.g., chronological aging or damage from environmental stressors (e.g., exposure to the sun). These signs may result from processes which include, but are not limited to, the development of textural discontinuities such as wrinkles, including both fine superficial wrinkles and coarse deep wrinkles, skin lines, crevices, bumps, pores and/or other forms of skin unevenness or roughness, sagging (including puffiness in the eye area, and jowls), loss of skin firmness, loss of skin tightness, loss of skin recoil, discoloration, blotching, sallowness, hyperpigmentation skin regions such as age spots and freckles, keratosis, hyperkeratinization, elastosis, collagen breakdown, and other histological changes in the stratum corneum, dermis, epidermis, the vascular system in the skin (e.g., telangiectasias), and underlying tissues, especially those proximate to the skin.

Minoxidil is a hydrophobic compound, which is readily commercially available and which has been incorporated into various compositions for topical (e.g., skin) application. Dosages are well known to those of ordinary skill in the art, but typically vary between 0.5% and 7% (w/w), preferably 2% to 5%, and more preferably about 5%. For example, ROGAINE® Topical Solution 5% contains minoxidil, at a concentration of 50 mg minoxidil per mL in a solution composed of alcohol, propylene glycol and water, and is typically applied twice daily although daily application is also used.

Various dosage forms are also well known. For example, foam formulations of minoxidil are known in the art. See, e.g., Shatalebi and Rafiei “Preparation and evaluation of minoxidil foamable emu oil emulsion,” Research in Pharmaceutical Sciences, 9(2): 123-133 (April 2014), the contents of which are incorporated herein by this reference.

Minoxidil is also commercially available as a foam formulation (Minoxidil topical foam, MTF), which is propylene glycol free. It is liquid (60 grams) pressurized in an aluminum can with a hydrocarbon propellant, which on valve actuation forms a foam lattice. This matrix is thermolabile and breaks down rapidly as soon as it comes into contact with skin. The volatile constituents evaporate and after a minute or so, little or no residue remains on the skin. This causes the active ingredient to concentrate at the vehicle-skin interface, and facilitates penetration
through the skin. Foam has the ability to deliver a greater amount of the active drug at an increased rate compared with other vehicles.

Preferably, the lower alkyl-substituted bicycloalkane is 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (available under the trade name ETHOCYN® from BCS Business Consulting Services Pte Ltd of Singapore) or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one. Methods of manufacture, and uses of skin care compositions comprising a lower alkyl-substituted bicycloalkane such as 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one ("ETHOCYN®") or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (CYOCTOL™) are described in great detail in U.S. Patents 4,689,349, 4,689,345, and 4,855,322.

These lower alkyl-substituted bicycloalkanes are non-steroidal competitive inhibitors for the 5-alpha dihydrotestosterone (DHT) and act to preserve collagen and, being inhibitors of 5-alpha dihydrotestosterone, independently act to prevent hair loss. See, e.g., C. Guttman, "New nonsteroidal antiandrogen topical benefits aging skin," *Dermatology Times*, 17(1):41 (Jan. 1996), the contents of which are incorporated herein by this reference, ("a nonsteroidal antiandrogen, (ETHOCYN®), which is clinically known as 6-(5-ethoxy-hept-1-yl) bicyclo[3.3.0]octan-3-one and helps to restore the elastic tissue in aging skin").

In certain embodiments, the composition reduces elastin degradation. This is especially useful in prophylactically treating loss of skin elasticity and tactile or visible signs of loss of skin elasticity associated with skin aging. Such signs of loss of elasticity include skin sagging, loss of skin firmness, loss of skin tightness and loss of skin recoil. The composition improves the function of elastin in the dermis. Without intending to be bound or otherwise limited by theory, it is believed that the loss of functional elastin results from the degradation of existing functional elastin, generally by the action of a proteolytic enzyme such as elastase.

The compositions may comprise a wide variety of optional components, provided that such optional components are physically and chemically compatible with the essential components described herein, and do not unduly impair stability, efficacy or other use benefits associated with the compositions of the disclosure.

In certain embodiments, the composition includes one or more additional ingredients. Such ingredients may include biotin, hair dye, catalase (see, e.g., U.S.
Patent 6,309,656 to Pugliese et al, October 31, 2001, the contents of which are incorporated herein by this reference, "PC-KUS" or pseudocatalase (see, e.g., U.S. Patent Publication No. 20030166570 to Woods et al, September 4, 2003, the contents of which are incorporated herein by this reference), solvents, thickeners, gelling agents, coloring materials, fillers, pigments, antioxidants, preservatives, fragrances, electrolytes, neutralizing agents, polymers, UV blocking agents, and combinations thereof.

For example, as previously identified, application of minoxidil is thought by some to increase the amount of a subject's gray hair. Thus, in certain embodiments, the method(s) and composition(s) for enhancing the appearance of the eyelashes and/or eyebrow(s) also includes changing (e.g., via a readily commercially available hair dye or hair colorant) or attempting to restore the natural pigmentation (e.g., by including, e.g., 2,000 IU to 4,000 IU catalase into the composition) of the subject's hair. The catalase and/or pseudocatalase is present in the composition such that there is an amount sufficient to bring back the natural pigmentation of at least some of the subject's hair. Such a method is effective in bringing back the natural pigmentation of hair if, e.g., its usage results in at least 15% of re-growing hair strands growing from the skin to which the composition has been applied having pigmentation (as opposed to lacking pigmentation, e.g., by being clear to gray).

Catalase is believed to work by breaking down hydrogen peroxide, which is also produced by our hair cells and which causes hair to lighten. In a July 2009 study by the Federation of American Societies for Experimental Biology, English researchers found that gray hair had lower-than-normal levels of catalase. Wood et al. "Senile hair graying: H_2O_2-mediated oxidative stress affects human hair color by blunting methionine sulfoxide repair," The FASEB Journal, 23(7):2065-2075 (2009), the contents of which are incorporated herein by this reference. PC-KUS or pseudocatalase cream is thought to work similarly, particularly when combined with the subsequent application of narrowband ultraviolet B light. See, e.g., Schallreuter et al. "Basic evidence for epidermal H_2O_2/ONOO^-mediated oxidation/nitration in segmental vitiligo is supported by repigmentation of skin and eyelashes after reduction of epidermal H_2O_2 with topical NB-UVB-activated pseudocatalase PC-KUS," FASEB J. 27(8):3113-22 (Aug. 2013).
Hair dyes are well known and described in the art. For example, European Directive 2012/21/EU (August 2, 2012), identifies various substances that can be used as hair dyes, and guidelines for their use including field of application, maximum authorized concentration in the finished cosmetic product, other limitations and requirements, and conditions of use and warnings to be printed on any associated labeling (e.g., resorcinol is not to be used to dye eyelashes or eyebrows).

For convenience or efficacy of application, the composition comprising the selected ingredients may be provided in various forms such as application stick, wand cream, mascara, eyebrow coloring, lotions, creams, aerosols, sprays, gels, foams, ointments, oils, mousse, emulsions, colloids, solutions, suspensions, spray-on formulations, brush-on formulations, hair spray, moisturizer, and combinations of any thereof. The ingredients may be incorporated into such forms via, e.g., liposomes, niosomes (see, e.g., Balakrishnan et al. "Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery," *International Journal of Pharmaceutics* 377:1-8 (2009)), or emulsions (see, e.g., Sakr et al. "Preparation and evaluation of a multimodal minoxidil microemulsion versus minoxidil alone in the treatment of androgenic alopecia of mixed etiology: a pilot study," *Drug Design, Development and Therapy*, 2013:7413-423 (May 2013)).

Particularly, when molecules of different hydrophobicity are present in the composition or formulation (e.g., relatively hydrophobic ETHOCYN® together with relatively hydrophilic pseudocatalase PC-KUS), a topical dosage form that can topically deliver both hydrophobic and hydrophilic molecules is preferred.

In some embodiments, the composition is formulated into a sustained-release formulation for transdermal application of the composition to the skin of a subject. A preferred sustained-release formulation is capable of maintaining active compounds of the composition at the skin, while permitting release of the compounds to the skin over an extended period of time (e.g., from about 6 to about 8 hours). Such a sustained-release formulation may comprise, for example, and without limitation: a high molecular weight alcohol (e.g., a polyvinyl alcohol having a molecular weight of at least 8000 Da). In a sustained-release formulation, the concentration of a lower alkyl-substituted bicycloalkane and minoxidil (e.g., an
anhydrous means for increasing collagen content of skin by topical application to the skin) may be higher than in a formulation for administration of these compounds without sustained-release. For example and without limitation, a sustained-release formulation may include from about 0.025% to about 3.00% (w/w) of a lower alkyl-substituted bicycloalkane. See, also, Gelfuso et al. "Chitosan microspheres for sustaining the topical delivery of minoxidil sulphate," J. Microencapsul., 28(7):650-658 (2011).

As previously identified, in certain embodiments, the formulation may include a percutaneous permeability enhancer to improve penetration of the composition into the dermis and dermal layers through the skin barrier represented by the epidermal stratum corneum.

Non-limiting examples of chemical permeability enhancers are: enzymes, cyclodextrins, liposomes, ehtosomes, sulfoxides, alcohols, fatty acids, fatty acid esters, amides surfactants, terpene, and/or alkanones organic acids. Specifically, these can be: ethanol, glyceryl monoethyl ether, monoglycerides, isopropylmyristate, lauryl alcohol (also, lauric acid, lauryl lactate), terpinol, menthol, D-limonene, beta-cyclodextrin, DMSO (dimethyl sulfoxide), polysorbates, fatty acids, e.g., oleic, N-methylpyrrolidone, polyglycosylated glycerides, 1-dodecylaza cycloheptan-2-one known as AZONE® (from Nelson Research and Development Company Corp.), cyclopentadecalactone known as CPE-215™, alkyl-2-(N,N-disubstituted amino)-alkanoate ester, known as NEXACT® (from NexMed, Inc. Corp.), 2-(n-nonyl)-1,3-dioxolane known as SEPA® (from MacroChem Corp).

Non-limiting examples of physical permeability enhancers can be microdermabrasion and/or dermabrasion. These physical permeability enhancers may be used alone or in combination with chemical permeability enhancers, as described above.

In certain embodiments, the formulation includes *P. sativum* sprout extracts which has been integrated into a cosmetic preparation for topical uses for the skin and/or hair of a human subject. The formulation comprises between 0.05% and 40% by weight, preferably between about 1% and 40% by weight, an extract of *P. sativum* in dehydrated form or not. *P. sativum* has been used in topical
preparations to act as a photoprotective agent in a cosmetic and/or pharmaceutical preparation for topical use. (see, e.g., U.S. Patent 6,184,199 to Pauly, February 6, 2001, and U.S. Patent 8,063,005 to Kalidindi, November 22, 2011). Pisum sativum sprout extract has been shown to initiate the growth of new hair by stimulating specific signaling molecules, Noggin (a protein that shortens the telogen phase) and FGF-7 (fibroblast growth factor-7 which promotes proliferation activity of the matrix keratinocytes to start a new anagen phase). D. Schmid, et al., *The FGF7 and Noggin genes are key targets to treat hair loss*, SOFW-journal, 139(9) at 18 (2013).

In certain embodiments, the formulation includes additional compounds including a bactericide, an antibiotic, an anti-microbial peptide, vitamin A, a vitamin A derivative, or a retinoid, and an inflammatory compound. Combinations with these types of compounds in combination with the formulation, provides effective treatments for skin disorders while reducing adverse effects in comparison to current treatments. The formulation may also decrease oil, or sebum, from sebaceous glands, reduce proliferation of sebocytes or inhibit or reduce sebocyte differentiation. The additional compounds may target bacteria colonies or will provide additional anti-inflammatory assistance as needed when treating a variety of skin disorders. Thus, the disclosure allows for the treatment of symptoms as well as modulation of pathways to prevent or limit the occurrence of skin disorders.

In certain embodiments, the additional components include aesthetic agents and other active agents. For example, the composition may include absorbents, abrasives, anticaking agents, antifoaming agents, antimicrobial agents, binders, biological additives, buffering agents, bulking agents, chemical additives, cosmetic biocides, denaturants, cosmetic astringents, drug astringents, external analgesics, film formers, humectants, opacifying agents, fragrances, pigments, colorings, essential oils, skin sensates, emollients, skin soothing agents, skin healing agents, pH adjusters, plasticizers, preservatives, preservative enhancers, propellants, reducing agents, additional skin-conditioning agents, skin penetration enhancing agents, dandruff therapies, skin protectants, solvents, suspending agents, emulsifiers, thickening agents, sunless tanning agents, antioxidants and/or radical scavengers, chelating agents, sequestrants, anti-acne agents, anti-inflammatory agents, depilation
agents, desquamation agents/exfoliants, organic hydroxyl acids, vitamins and derivatives thereof, and other natural extracts.

In certain embodiments, the composition may be applied to other areas of human skin, such as, for example, the beard region or the mustache region of a man. Although, this would be a lifetime product, since hair regularly turns over, coloring of the eyebrow and use for a lifetime is usually necessary. Via one's methods may decrease the density of hair (e.g., the number of hairs per cm² of skin) that is growing in a given area of the human body (e.g., eyebrow or eyelashes) as compared to the density of hair present in a similar area of the same person's body to which the method has not been applied.

Preferably, applying the composition to the skin is done carefully to ensure that the topical composition is substantially applied only to the skin and to avoid applying the topical composition to the hair (e.g., more than 90% or 95% of the topical composition is applied to the skin or less than 5% of the topical composition has contact with the outer 50% of the length of the hair strands). When the human hair being treated includes eyelashes, the step of applying the composition may include, e.g., application of the topical composition to an area including an eyelid in the immediate vicinity of the normal lash line, eyelashes, and the base of the eyelash.

Although something as relatively simple as a dropper can be effectively used to apply a liquid formulation hereof and may be preferred at times, other delivery means may be preferred at other times because, e.g., with application to the eyebrows, a liquid formulation could run into the subject's eye(s). For instance, while the liquid dropper methods of application certainly saturate the scalp better, having a liquid run down one's face into the eyes and also wetting the hair is not what one wants when rushing out to work or school in the morning.

The composition can be administered directly without any carrier. It can also be formulated into dermatological or cosmetic carriers.

Referring to FIG. 1, in use, a woman could choose to apply a liquid formulation via dropper (not shown) in the evening, and a wand 12, 16 or stick 14 in the daytime (with a color or dye as part of the formulation) to fill in the eyebrow while at the same time causing it to eventually become thicker with hair content. Although, this would be a lifetime product, since hair regularly turns over, coloring of the eyebrow and use.
of eyelash wands are parts of a regular regimen of many self-grooming people, so daily lifetime application should not be inconvenient.

A wand 12 is typically used to, e.g., apply color onto scalp hair at the roots in order to cover gray hair. People do not want to dye their hair too often, because hair dyes can be harsh and too frequent of use of them may cause hair to break off and/or fall out. Wands are better applicators for the brows and eyelashes.

A stick 12 is also used to cover gray hair. A stick formulation comprising, in its reservoir 10, minoxidil, ETHOCYN®, ethocyn, and optionally catalase and other ingredients (e.g., P. sativum) may be used for enhancing scalp hair. Thus, such a stick formulation forms a part of the disclosure.

Such a stick formulation also including temporary hair color can ideally be used to cover gray color. In certain embodiments, people using a stick comprising hair color use these hair color sticks and wands for the roots of scalp hair to cover gray "grow-in" until the person goes to, e.g., a hairdresser (or has time at home) to use a dye to cover gray scalp hairs.

In certain embodiments, the person using formulations hereof use the colored wand or stick in the morning application and the liquid at night before going to sleep. The liquid dropper saturates the scalp, but the wand or stick is a more controlled application as previously described.

The second depicted wand 16 and 18, 18 is typically used for the eyebrows. It can come in a spectrum of hair colors (e.g., brown, black, auburn, blond, and clear) and makes the brows look thick and groomed while coloring over gray in the brows. Thus, in certain embodiments, the formulation including the ingredients (e.g., minoxidil, ETHOCYN®, and optionally catalase, pseudocatalase, Pisum sativum sprout extract, and/or hair dye or color) is contained within reservoir portion 18 for eventual application by the wand 16.

Mascara wands (not shown) are readily commercially available and suitable for application of the formulation to the eyelash(s) to enhance and/or thicken growth.

The contents of each of the publications, patents, and patent applications referenced herein are incorporated herein in their entirety by this reference.

The invention is further described with the aid of the following illustrative examples.
EXAMPLES

Example I

A foam as described in U.S. Patent Publication 20050079139 to Jacques, April 14, 2005, "Minoxidil pharmaceutical foam formulation," the contents of which are incorporated herein by this reference, is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (available under the trade name ETHOCYN® from BCS Business Consulting Services Pte Ltd of Singapore).

Example II

The foam of example I is applied twice daily to the eyebrows of a mature woman experiencing thinning eyebrows for three months. Eyebrow growth reoccurs increasing the density of hair, and the eyebrows thicken, thus enhancing the subject's eyebrows' appearance.

Example III

A foam as described in the incorporated Shatalebi and Rafiei "Preparation and evaluation of minoxidil foamable emu oil emulsion," Research in Pharmaceutical Sciences, 9(2):123-133 (April 2014), the contents of which are incorporated herein by this reference, is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (ETHOCYN®) and pseudocatalase (2.5 grams - 3 grams of PC-KUS powder to 3ml (about 1/2 teaspoon) of distilled water for incorporation into the water phase of the composition).

Example IV

A foam as described in the incorporated Shatalebi and Rafiei "Preparation and evaluation of minoxidil foamable emu oil emulsion," Research in Pharmaceutical Sciences, 9(2):123-133 (April 2014), is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (ETHOCYN®) and pseudocatalase (2.5 grams - 3 grams of PC-KUS powder to 3ml (about 1/2 teaspoon) of distilled water for incorporation into the water phase of the composition). In addition, the formulation also includes P. sativum sprout extract
that when applied to the scalp of a human subject is present in an amount between about 1% and about 40% by weight (e.g., 25%).

Example V

The foam of example III is applied twice daily to the eyebrows of a mature woman experiencing thinning eyebrows for four months. Eyebrow growth reoccurs increasing the density of hair, and the eyebrows thicken, and the hair color of the eyebrows returns to that of the subject's natural hair color, enhancing the eyebrows' appearance.

Example VI

A nanostructured lipid carrier (NLC) gel as described in Uprit et al. "Preparation and characterization of minoxidil loaded nanostructured lipid carrier gel for effective treatment of alopecia," Saudi Pharm. J, 21(4):379-85 (Oct. 2013), the contents of which are incorporated herein by this reference, and having controlled or sustained release characteristics is formulated, but also includes 0.050% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (ETHOCYN®), P. sativum sprout extract, and catalase.

Example VII

The nanostructured lipid carrier (NLC) gel of example V is applied once daily to the eyebrows of a woman experiencing thinning eyelashes and eyebrows for three months. Eyelash and eyebrow growth reoccurs increasing the density of hair, the eyelashes and eyebrows thicken, and the hair color of the eyebrows returns to that of the subject's natural hair color, enhancing the eyebrows' appearance.

Example VIII

A foam as described in the incorporated Shatalebi and Rafiei "Preparation and evaluation of minoxidil foamable emu oil emulsion," Research in Pharmaceutical Sciences, 9(2):123-133 (April 2014), the contents of which are incorporated herein by this reference, is formulated, but also includes 0.025%
6-(5-ethoxyhept-l-yl)bicyclo[3.3.0]octan-3-one (ETHOCYN®), *P. sativum* sprout extract, and hair dye selected to match the natural hair color of a subject.

Example IX

The foam of example VII is applied twice daily to the eyebrows of a mature woman experiencing thinning eyebrows for three months. Eyebrow growth reoccurs increasing the density of hair, and the eyebrows thicken, and the hair color of the eyebrows returns to that of the subject's natural hair color, enhancing the eyebrows' appearance.

Example X

A nanostructured lipid carrier (NLC) gel as described in the incorporated Uprit et al. "Preparation and characterization of minoxidil loaded nanostructured lipid carrier gel for effective treatment of alopecia," *Saudi Pharm. J.*, 21(4):379-85 (Oct. 2013), the contents of which are incorporated herein by this reference, and having controlled or sustained release characteristics is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (ETHOCYN®) and a hair colorant selected to mask a subject's gray eyebrow hair. The NLC formulation is packaged within reservoir 18 of FIG. 1.

Example XI

The NLC gel of example IX is applied with wand 16 of FIG. 1 in the mornings to the eyebrows of a human subject experiencing thinning eyebrows for three months. Before bedtime, the subject applies a clear, liquid alcohol solution of minoxidil 5% together with ETHOCYN®, and *P. sativum* sprout extract, and pseudocatalase, as described herein. Eyebrow growth reoccurs, increasing the density of hair, the eyebrows thicken, and the hair color of the eyebrows returns to that of the subject's natural hair color, enhancing the eyebrows' appearance.

Example XII

A man is identified as having thinning and greying hair in the beard and/or mustache region of his face. Where the man applies any of a foam, gel, or both
disclosed, in the examples III, IV, X, or XI, once or twice daily to the thinning and/or greying beard region of his face for one to three months. Bread hair growth reoccurs increasing the density of hair, the graying hair is colored, and the facial hair thickens, thus, the subject's appearance is enhanced.

Example XIII
A foam as described in the incorporated U.S. Patent Publication No. 2005/0079139 to Jacques (April 14, 2005), "Minoxidil pharmaceutical foam formulation," the contents of which are incorporated herein by this reference, is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (available under the trade name ETHOCYN® from BCS Business Consulting Services Pte Ltd of Singapore) and P. sativum sprout extract which when applied to the scalp of a human subject is present in an amount between about 1% and about 40% by weight (e.g., 30%).

Example XIV
A gel as described in WIPO Patent Publication No. WO/2011/080743 to Bachar (December 30, 2010), "Alcohol gel for reducing hair growth," the contents of which are incorporated herein by this reference, is formulated, but also includes 0.025% 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one (available under the trade name ETHOCYN® from BCS Business Consulting Services Pte Ltd Corp. of Singapore).
What is claimed is:

1. A composition comprising:
   an amount of minoxidil sufficient to increase the growth of eyelashes and/or eyebrow(s) in a human subject;
   an amount of a lower alkyl-substituted bicycloalkane sufficient to increase the growth of eyelashes and/or eyebrow(s) in a human subject and to inhibit collagen destruction caused by the minoxidil; and
   a cosmetically acceptable carrier.

2. The composition of claim 1, wherein the composition further comprises means for coloring hair.

3. The composition of claim 1 or claim 2, wherein the lower alkyl-substituted bicycloalkane is 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one or 6-(5-methoxyhept-1-yl)bicyclo[3.3.0]octan-3-one.

4. The composition of claim 1, claim 2, or claim 3, further comprising catalase and/or pseudocatalase in an amount sufficient to bring back the natural pigmentation of the subject's hair.

5. The composition of claim 1, claim 2, claim 3, or claim 4, wherein the lower alkyl-substituted bicycloalkane is present in an amount between about 0.001% and about 5.000% (w/w).

6. The composition of claim 1, claim 2, claim 3, or claim 4, or claim 5, wherein the minoxidil is present in an amount between about 2% and about 5%.
7. The composition of claim 1, claim 2, claim 3, or claim 4, claim 5, or claim 6, further comprising an amount of *Pisum sativum* sprout extract sufficient to increase the growth or restoration of hair in a human subject.

8. A topical formulation for enhancing the eyelashes and/or eyebrow(s) of a subject, the topical formulation comprising the composition of any one of the preceding claims.

9. The topical formulation of claim 8, wherein the formulation is selected from the group consisting of a solid, an ointment, an oil, a lotion, a cream, a gel, a foam, a mousse, an aerosol, and a liquid.

10. The topical formulation of claim 8 or claim 9, wherein the formulation is a sustained-release formulation.

11. The topical formulation of claim 8, claim 9, or claim 10, wherein the topical formulation when applied to the skin of a subject, reduces existing wrinkles in the skin and/or decreases the appearance of new wrinkles in the skin over time, as compared to an otherwise identical topical formulation lacking the lower alkyl-substituted bicycloalkane.

12. The topical formulation of any one of claims 8 - 11, wherein the lower alkyl-substituted bicycloalkane is present in an amount between about 0.001% and about 5.000% (w/w).

13. The topical formulation of any one of claims 8 - 12, wherein the minoxidil is present in an amount between about 2% and about 5%.

14. In a cosmetic method of enhancing the appearance of eyelashes and/or eyebrow(s) of a subject by topically applying a composition comprising minoxidil to the eyelash and/or eyebrow area, the improvement comprising:
incorporating into the composition a sufficient amount of lower alkyl-substituted bicycloalkane to increase hair growth of eyelashes and/or eyebrow(s) when applied topically to the subject and to reduce collagen destruction in the subject's skin caused by the minoxidil.

15. The cosmetic method according to claim 14, wherein the lower alkyl-substituted bicycloalkane is 6-(5-ethoxyhept-1-yl)bicyclo[3.3.0]octan-3-one.

16. The cosmetic method according to claim 14 or claim 15, comprising improving the appearance of the subject's skin by reducing existing wrinkles in the skin and/or a decrease in the appearance of new wrinkles in the skin.

17. The cosmetic method according to any one of claims 14 - 16, wherein the composition further comprises catalase and/or pseudocatalase in an amount sufficient to bring back the natural pigmentation of the subject's hair.

18. The cosmetic method according to any one of claims 14 - 17, wherein the composition further comprises a hair dye and/or hair color in an amount sufficient to color the subject's hair.

19. A sustained release formulation for once a day application for enhancing the eyelashes and/or eyebrow(s) of a subject, the topical formulation comprising:

- an amount of minoxidil sufficient to increase the growth of eyelashes and/or eyebrow(s) in a human subject upon prolonged daily application;
- an amount of a lower alkyl-substituted bicycloalkane sufficient to increase the growth of eyelashes and/or eyebrow(s) in a human subject and to inhibit collagen destruction caused by the minoxidil upon prolonged daily application; and
- a cosmetically acceptable carrier.
20. The sustained release formulation of claim 19, further comprising: catalase and/or pseudocatalase present in the composition in an amount sufficient to bring back and/or preserve the natural pigmentation of the subject's hair during treatment with the sustained release formulation, and/or a hair dye and/or hair colorant selected to match a desired hair color of the subject.

21. The sustained release formulation of claim 19 or claim 20, wherein the formulation is selected from the group consisting of a solid, an ointment, an oil, a lotion, a cream, a gel, a foam, a mousse, an aerosol, and a liquid.

22. The sustained release formulation of any one of claims 19 - 21, wherein the lower alkyl-substituted bicycloalkane is present in an amount between about 0.001% and about 5.000% (w/w) and the minoxidil is present in an amount between about 2% and about 5% (w/w).

23. A wand for topical administration of a formulation of the type associated with a reservoir containing the formulation, wherein the formulation is the formulation of claim 8 or 19.

22. A stick for topical administration of a formulation of the type associated with a reservoir containing the formulation for administration by the stick, wherein the formulation is the formulation of claim 8 or claim 19.

23. A dropper for topical administration of a formulation of the type associated with a reservoir bottle containing the formulation, wherein the formulation is the formulation of claim 8 or 19.