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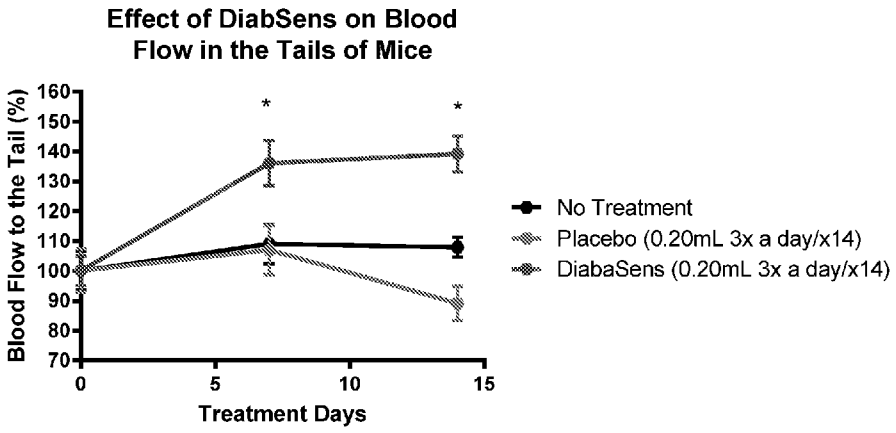


FIGURE 1

(57) Abstract: Topical compositions comprising L-arginine and L-citrulline are described. Methods and uses are also provided that include the administration of an effective amount of the topical compositions. The topical compositions are useful for increasing sensitization of the skin and/or for increasing blood flow to the skin.

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SENSITIZATION CREAM COMPRISING L-ARGININE AND L-CITRULLINE AND THERAPEUTIC USES THEREOF

Background of the Invention

Field of the Invention

[0001] The present invention generally relates to a method and topical composition for improving blood flow to the skin and improving sensitivity of the skin. More specifically, the present invention relates to a topical formulation for increasing sensitization wherein the formulation comprises L-arginine and L-citrulline.

Description of the Related Art

[0002] The penis is a highly sensitive organ that contains thousands of nerve ending. In order for sexual arousal to occur, these nerve endings need to be stimulated. When a loss of sensation occurs, it can be more difficult for men to become aroused, reach orgasm, and enjoy sexual activity. This loss of sensitivity can lead to an inability to enter relationships, can cause strain in relationships, reduce a partner's sexual satisfaction, and can cause psychological damage to sufferers.

[0003] A number of factors can lead to reduced penis sensitivity. Poor circulation attributable to poor cardiovascular health, or neuropathy, including peripheral neuropathy caused by systemic disorders such as diabetes (also known as diabetic neuropathy) or by hyperglycemia-induced glycation, the effect of certain medications, or traumatic injury. Other factors that can lead to reduced penis sensitivity include lack of exercise, and obesity. Drug and alcohol use, smoking, use of prescription medication such as anti-depressants, and aging are also thought to contribute to a loss of penile sensation. Additionally, circumcision may also impair penile sensation due to the removal of highly sensitive foreskin tissue.

[0004] Efforts to improve penile sensitivity have been directed toward optimizing other aspects of health, such as reducing body weight and quitting smoking. For circumcised men, foreskin restoration options may be available, however such procedures have mixed results and unwanted side effects. In particular, surgical restoration procedures may be

highly risky and be prohibitively expensive for most men. Topical creams are also available for increasing penis sensitivity due to the ease of application and low cost compared with other treatment options. Examples of sensitization creams are disclosed in U.S. Patent Nos. 9,821,021 and 9,833,488.

[0005] Improving blood flow to the penis can also enhance its function, improve symptoms of erectile dysfunction and enhance sexual arousal. U.S. Patent No. 5,439,938 discloses a method for treating male comprising a compound that generates nitric oxide in an amount sufficient to initiate penile erection. Also, infusion of L-arginine, a precursor to nitric oxide in the body, promotes vasodilation and blood flow (*See* Morikawa *et al*, Stroke 1994; 25:429-435). Topical delivery of arginine to produce enhanced blood flow in the penis is disclosed in U.S. Patent No. 7,914,814.

[0006] Diabetic neuropathies are a family of nerve disorders caused by diabetes. People with diabetes can, over time, develop nerve damage throughout the body, and nerve problems can occur in every organ system, including the digestive tract, heart, and sex organs. About 60 to 70 percent of people with diabetes have some form of neuropathy, and the neuropathy can cause loss of sensitivity in the feet and hands and can result in changes in sexual response, such an inability to have erections or reach sexual climax. Increasing sensitivity of the remaining nerves of neuropathy patients may result in increased sensation, ease the symptoms of neuropathy, and greatly improve a person's quality of life. An example of the treatment of neuropathy by topical application of a composition is described in U.S. Patent Publication No. 2003/0157185.

[0007] Thus there is a need for a method of increasing sensitivity of the penis and blood flow to the penis that requires no specialized therapy, can be used easily, conveniently, and without embarrassment, and does not involve the problems associated with prior therapeutic methods.

Summary of the Invention

[0008] Some embodiments of disclosed invention provide a topical composition for improving the sensitivity of the skin and improving blood flow to the skin comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion.

[0009] In some embodiments, the composition comprises about 6 wt. % sweet almond oil, about 0.75 wt. % cinnamon bark oil, about 0.5 wt. % coriander seed oil, about 0.34 wt. % L-arginine, and about 0.68 wt. % L-citrulline.

[0010] In some embodiments, the mass ratio of L-arginine to L-citrulline in the composition is about 1:2.

[0011] In some embodiments, the mass ratio of sweet almond oil to cinnamon bark oil to coriander seed oil to L-arginine to L-citrulline in the composition is about 72:9:6:4:8.

[0012] In some embodiments, the composition further comprises one or more pharmaceutically acceptable excipients.

[0013] In some embodiments, the composition comprises: about 6 wt. % sweet almond oil, about 0.75 weight percent cinnamon bark oil, about 0.5 wt. % coriander seed oil, about 0.34 wt. % L-arginine, about 0.68 wt. % L-citrulline, about 5.0 wt. % of a 70 percent by weight sorbitol solution in water, about 4.0 wt. % of a 70 percent by weight isopropyl alcohol solution in water, about 20.0 wt. % propylene glycol, about 1.0 wt. % butylated hydroxytoluene, about 1.0 wt. % triethanolamine, about 1.0 wt. % benzyl alcohol, about 1.0 wt. % benzyl benzoate, about 3.5 wt. % PEG 40-hydrogenated castor oil, about 1.3 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer, about 0.1 wt. % ethylenediaminetetraacetic acid disodium salt, and about 53.9 wt. % water.

[0014] Other embodiments disclosed herein include a method of improving the sensitivity of the skin or improving blood flow to the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion. In some embodiments, the method disclosed herein improves the sensitivity of the skin. In some embodiments, the method disclosed herein improves the blood flow to the skin. In some embodiments, the method disclosed herein improves and or provides at least partial relief for one or more symptom of neuropathy. In some embodiments, the method disclosed herein improves and or provides at least partial relief for one or more symptom of diabetic neuropathy. In some embodiments, the method disclosed herein improves the sensitivity of the skin and the blood flow to the skin. In some embodiments, the method disclosed herein improves the sensitivity of the skin and the symptoms of diabetic neuropathy. In some

embodiments, the method disclosed herein improves the blood flow to the skin and the symptoms of diabetic neuropathy. In some embodiments, the method disclosed herein improves the sensitivity of the skin, the blood flow to the skin, and the symptoms of diabetic neuropathy.

[0015] In some embodiments, the composition is applied to the skin of the human penis. In some embodiments penis is circumcised. In some embodiments, the penis is uncircumcised. In some embodiments, a dose of approximately 0.5 mL, 0.6 mL, 0.7 mL, 0.8 mL, 0.9 mL, 1.0 mL, 1.1 mL, 1.2 mL, 1.3 mL, 1.4 mL, 1.5 mL, 2.0 mL, 2.5 mL, 3.0 mL, 3.5 mL, 4.0 mL, 4.5 mL, 5.0 mL or more of the composition are applied topically to the skin one or, more preferably, two to three times daily for a period of one week or, more preferably, two to three weeks to have an initial loading dose of the composition, followed by one to two applications daily or as needed.

Brief Description of the Drawings

[0016] FIGURE 1 describes the effect of the formulation disclosed herein on blood flow in the tails of mice.

[0017] FIGURE 2 describes the effect of the formulation disclosed herein on topical pain in mice after 14 days of treatment in the Tail Flick Heat Model.

Detailed Description of the Preferred Embodiment

[0018] In some embodiments, a topical composition is provided comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline. In some embodiments, the topical composition is formulated as an oil-in water emulsion. The topical compositions may be formulated as, for example, a gel, lotion, cream, mousse, aerosol, ointment, or lubricants, etc., so long as when the composition is applied, especially to the genitalia, the formulation will substantially stay in place. For example, there will not be substantial run-off, for a sufficient time after application, to permit an individual to spread the composition over a relevant portion of the penis, preferably, over the glans of the penis.

[0019] In some embodiments, the topical compositions comprises sweet almond oil in any amount up to its solubility limit. In some embodiments, the amount of sweet almond oil in the topical composition may be, for example, at least 1.0 wt. %, at least 2.0 wt.

%, at least 3.0 wt. %, at least 4.0 wt. %, at least 5.0 wt. %, at least 6.0 wt. %, at least 7.0 wt. %, at least 8.0 wt. % at least 9.0 wt. %, or at least 10.0 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 1.0 wt. %, 1.5 wt. %, 2.0 wt. %, 2.5 wt. %, 3.0 wt. %, 3.5 wt. %, 4.0 wt. %, 4.5 wt. %, 5.0 % wt. %, 5.5 wt. %, 6.0 wt. %, 6.5 wt. %, 7.0 wt. %, 7.5 wt. %, 8.0 wt. %, 8.5 wt. %, 9.0 wt. %, 9.5 wt. %, and 10.0 wt. % sweet almond oil present in the topical composition are contemplated within the scope of the invention.

[0020] In some embodiments, the topical compositions comprises cinnamon bark oil in any amount up to its solubility limit. In some embodiments, the amount of cinnamon bark oil in the topical composition may be, for example, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.75 wt. %, at least 1.0 wt. %, at least 1.25 wt. %, at least 1.5 wt. %, at least 1.75 wt. %, at least 2.0 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.1 wt. %, 0.2 wt. %, 0.3 wt. %, 0.4 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, 1.0 wt. %, 1.05 wt. %, 1.10 wt. %, 1.15 wt. %, 1.20 wt. %, 1.25 wt. %, 1.50 wt. %, 1.75 wt. %, and 2.0 wt. % cinnamon bark oil present in the topical composition are contemplated within the scope of the invention.

[0021] In some embodiments, the topical compositions comprises coriander seed oil in any amount up to its solubility limit. In some embodiments, the amount of coriander seed oil in the topical composition may be, for example, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.75 wt. %, at least 1.0 wt. or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.1 wt. %, 0.15 wt. %, 0.2 wt. %, 0.25 wt. %, 0.3 wt. %, 0.35 wt. %, 0.4 wt. %, 0.45 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, and 1.0 wt. % coriander seed oil present in the topical composition are contemplated within the scope of the invention.

[0022] In some embodiments, the topical compositions comprises L-arginine in any amount up to its solubility limit. In some embodiments, the amount of L-arginine in the topical composition may be, for example, at least 0.001 wt. %, at least 0.002 wt. %, at least 0.005 wt. %, at least 0.01 wt. %, at least 0.02 wt. %, at least 0.03 wt. %, at least 0.05 wt. %, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %,

at least 1.0 wt. %, at least 2.0 wt. %, at least 3.0 wt. %, at least 4.0 wt. %, at least 5.0 wt. %, or at least 6.0 wt. % or within a range defined by any two of the aforementioned concentrations. For example, in some embodiments, the amount of L-arginine present in the topical composition will range from, for example, approximately 0.05 wt. % to approximately 5.0 wt. %, from approximately 0.2 wt. % to approximately 3.0 wt. %, from approximately 0.001 wt. % to approximately 0.01 wt. %, from approximately 0.01 wt. % to approximately 0.05 wt. %, from approximately 0.05 wt. % to approximately 0.10 wt. %, or from approximately 0.20 wt. % to approximately 0.60 wt. %. Approximately 0.1 wt. %, 0.2 wt. %, 0.3 wt. %, 0.33 wt. %, 0.67 wt. %, 1.0 wt. %, 1.33 wt. %, 1.67 wt. %, 2.0 % wt. 2.33 wt. %, 2.67 wt. %, 3.0 wt. %, 4.0 wt. %, and 5.0 wt. % L-arginine present in the topical composition are contemplated within the scope of the invention.

[0023] In some embodiments, the topical compositions provided herein may comprise L-citrulline in any amount up to its solubility limit. In some embodiments, the amount of L-citrulline in the topical composition may be, for example, at least 0.001 wt. %, at least 0.002 wt. %, at least 0.005 wt. %, at least 0.01 wt. %, at least 0.02 wt. %, at least 0.03 wt. %, at least 0.05 wt. %, at least 0.10 wt. % at least 0.20 wt. % at least 0.30 wt. % at least 0.40 wt. % , at least 0.50 wt. % at least 0.60 wt. %, at least 0.70 wt. %, at least 0.80 wt. %, at least 0.90 wt. %, at least 1.0 wt. %, at least 2.0 wt. %, at least 3.0 wt. %, at least 4.0 wt. %, at least 5.0 wt. %, at least 6.0 wt. %, at least 7.0 wt. %, at least 8.0 wt. %, or within a range defined by any two of the aforementioned concentrations. For example, in some embodiments, the amount of L-citrulline present in the topical composition ranges from, approximately 0.1 wt. % to approximately 8.0 wt. %, from approximately 0.1 wt. % to approximately 6.0 wt. %, from approximately 0.001 wt. % to approximately 0.01 wt. %, from approximately 0.01 wt. % to approximately 0.05 wt. %, from approximately 0.1 wt. % to approximately 0.10 wt. %, or from approximately 0.40 wt. % to approximately 0.80 wt. %. Approximately 0.1 wt. %, 0.2 wt. %, 0.3 wt. %, 0.33 wt. %, 0.67 wt. %, 1.0 wt. %, 1.33 wt. %, 1.67 wt. %, 2.0 % wt. 2.33 wt. %, 2.67 wt. %, 3.0 wt. %, 4.0 wt. %, 5.0 wt. %, 6.0 wt. %, 7.0 wt. %, and 8.0 wt. % L-citrulline present in the topical composition are contemplated within the scope of the invention.

[0024] In some embodiments, the topical compositions comprises sorbitol solution USP 70%in any amount up to its solubility limit. In some embodiments, the amount

of sorbitol solution USP 70% in the topical composition may be, for example, at least 1.0 wt. %, at least 2.0 wt. %, at least 3.0 wt. %, at least 4.0 wt. %, at least 5.0 wt. %, at least 6.0 wt. %, at least 7.0 wt. %, at least 8.0 wt. %, at least 9.0 wt. %, at least 10.0 wt.%, or within a range defined by any two of the aforementioned concentrations. Approximately 1.0 wt. %, 1.5 wt. %, 2.0 wt. %, 2.5 wt. %, 3.0 wt. %, 3.5 wt. %, 4.0 wt. %, 4.5 wt. %, 5.0 wt. %, 5.5 wt. %, 6.0 wt. %, 6.5 wt. %, 7.0 wt. %, 7.5 % wt. %, 8.0 wt. %, 8.5 wt. %, 9.0 wt. %, , 9.5 wt. %, and 10.0 wt. % sorbitol solution USP 70% present in the topical composition are contemplated within the scope of the invention.

[0025] In some embodiments, the topical compositions comprises isopropyl alcohol USP 70% in any amount up to its solubility limit. In some embodiments, the amount of isopropyl alcohol USP 70% in the topical composition may be, for example, at least 1.0 wt. %, at least 2.0 wt. %, at least 3.0 wt. %, at least 4.0 wt. %, at least 5.0 wt. %, at least 6.0 wt. %, at least 7.0 wt. %, at least 8.0 wt. %, at least 9.0 wt. %, at least 10.0 wt.%, or within a range defined by any two of the aforementioned concentrations. Approximately 1.0 wt. %, 1.5 wt. %, 2.0 wt. %, 2.5 wt. %, 3.0 wt. %, 3.5 wt. %, 4.0 wt. %, 4.5 wt. %, 5.0 wt. %, 5.5 wt. %, 6.0 wt. %, 6.5 wt. %, 7.0 wt. %, 7.5 % wt. %, 8.0 wt. %, 8.5 wt. %, 9.0 wt. %, , 9.5 wt. %, and 10.0 wt. % isopropyl alcohol USP 70% present in the topical composition are contemplated within the scope of the invention.

[0026] In some embodiments, the topical compositions comprises propylene glycol in any amount up to its solubility limit. In some embodiments, the amount of propylene glycol in the topical composition may be, for example, at least 10 wt. %, at least 15 wt. %, at least 20 wt. %, at least 25 wt. %, at least 30 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 15.0 wt. %, 16.0 wt. %, 17.0 wt. %, 18.0 wt. %, 19.0 wt. %, 20.0 wt. %, 21.0 wt. %, 22.0 wt. %, 23.0 wt. %, 24.0 wt. %, 25.0 wt. %, 26.0 wt. %, 27.0 wt. %, 28.0 % wt. %, 29.0 wt. %, and 30.0 wt. % propylene glycol present in the topical composition are contemplated within the scope of the invention.

[0027] In some embodiments, the topical compositions comprises butylated hydroxytoluene in any amount up to its solubility limit. In some embodiments, the amount of butylated hydroxytoluene in the topical composition may be, for example, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.6 wt. %, at least 0.7 wt. %, at least 0.8 wt. %, at least 0.9 wt. %, at least 1.0 wt. %, at least 1.1 wt.

%, at least 1.2 wt. % at least 1.3 wt. %, at least 1.4 wt. %, , at least 1.5 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.1 wt. %, 0.15 wt. %, 0.2 wt. %, 0.25 wt. %, 0.3 wt. %, 0.35 wt. %, 0.4 wt. %, 0.45 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, 1.0 wt. %, %, 1.05 wt. %, 1.10 wt. %, 1.15 wt. %, 1.20 % wt. %, 1.25 wt. %, 1.30 wt. %, 1.35 wt. %, 1.40 wt. %, %, 1.45 wt. %, and 1.50 wt. % butylated hydroxytoluene present in the topical composition are contemplated within the scope of the invention.

[0028] In some embodiments, the topical compositions comprises triethanolamine in any amount up to its solubility limit. In some embodiments, the amount of triethanolamine in the topical composition may be, for example, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.6 wt. %, at least 0.7 wt. %, at least 0.8 wt. %, at least 0.9 wt. %, at least 1.0 wt. %, at least 1.1 wt. %, at least 1.2 wt. % at least 1.3 wt. %, at least 1.4 wt. %, , at least 1.5 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.1 wt. %, 0.15 wt. %, 0.2 wt. %, 0.25 wt. %, 0.3 wt. %, 0.35 wt. %, 0.4 wt. %, 0.45 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, 1.0 wt. %, %, 1.05 wt. %, 1.10 wt. %, 1.15 wt. %, 1.20 % wt. %, 1.25 wt. %, 1.30 wt. %, 1.35 wt. %, 1.40 wt. %, %, 1.45 wt. %, and 1.50 wt. % triethanolamine present in the topical composition are contemplated within the scope of the invention.

[0029] In some embodiments, the topical compositions comprises benzyl alcohol in any amount up to its solubility limit. In some embodiments, the amount of benzyl alcohol in the topical composition may be, for example, at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.6 wt. %, at least 0.7 wt. %, at least 0.8 wt. %, at least 0.9 wt. %, at least 1.0 wt. %, at least 1.1 wt. %, at least 1.2 wt. % at least 1.3 wt. %, at least 1.4 wt. %, , at least 1.5 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.1 wt. %, 0.15 wt. %, 0.2 wt. %, 0.25 wt. %, 0.3 wt. %, 0.35 wt. %, 0.4 wt. %, 0.45 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, 1.0 wt. %, %, 1.05 wt. %, 1.10 wt. %, 1.15 wt. %, 1.20 % wt. %, 1.25 wt. %, 1.30 wt. %, 1.35 wt. %, 1.40 wt. %, %, 1.45 wt. %, and 1.50 wt. % benzyl alcohol present in the topical composition are contemplated within the scope of the invention.

[0030] In some embodiments, the topical compositions comprises benzyl benzolate in any amount up to its solubility limit. In some embodiments, the amount of benzyl benzolate in the topical composition may be, for example at least 0.1 wt. %, at least 0.2 wt. %, at least 0.3 wt. %, at least 0.4 wt. %, at least 0.5 wt. %, at least 0.6 wt. %, at least 0.7 wt. %, at least 0.8 wt. %, at least 0.9 wt. %, at least 1.0 wt. %, at least 1.1 wt. %, at least 1.2 wt. % at least 1.3 wt. %, at least 1.4 wt. %, , at least 1.5 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.1 wt. %, 0.15 wt. %, 0.2 wt. %, 0.25 wt. %, 0.3 wt. %, 0.35 wt. %, 0.4 wt. %, 0.45 wt. %, 0.5 wt. %, 0.55 wt. %, 0.60 wt. %, 0.75 wt. %, 0.80 % wt. %, 0.85 wt. %, 0.90 wt. %, 0.95 wt. %, 1.0 wt. %, %, 1.05 wt. %, 1.10 wt. %, 1.15 wt. %, 1.20 % wt. %, 1.25 wt. %, 1.30 wt. %, 1.35 wt. %, 1.40 wt. %, %, 1.45 wt. %, and 1.50 wt. % benzyl benzolate present in the topical composition are contemplated within the scope of the invention.

[0031] In some embodiments, the topical compositions comprises PEG 40-hydrogenated castor oil in any amount up to its solubility limit. In some embodiments, the amount of PEG 40-hydrogenated castor oil in the topical composition may be, for example, at least 1.5 wt. %, at least 2.0 wt. %, at least 2.5 wt. %, at least 3.0 wt. %, at least 3.5 wt. %, at least 4.0 wt. %, at least 4.5 wt. %, at least 5.0 wt. %, at least 5.5 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 1.5 wt. %, 2.0 wt. %, 2.5 wt. %, 3.0 wt. %, 3.5 wt. %, 4.0 wt. %, 4.5 wt. %, 5.0 wt. %, and 5.5 wt. % PEG 40-hydrogenated castor oil present in the topical composition are contemplated within the scope of the invention.

[0032] In some embodiments, the topical compositions comprises acrylate/C_{10-30} alkyl acrylate crosspolymer in any amount up to its solubility limit. In some embodiments, the amount of acrylate/C_{10-30} alkyl acrylate crosspolymer in the topical composition may be, for example, at least 0.5 wt. %, at least 1.0 wt. %, at least 1.5 wt. %, at least 2.0 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.5 wt. %, 0.6 wt. %, 0.7 wt. %, 0.8 wt. %, 0.9 wt. %, 1.0 wt. %, 1.1 wt. %, 1.2 wt. %, 1.3 wt. %, 1.4 wt. %, 1.5 wt. %, 1.6 wt. %, 1.7 wt. %, 1.8 wt. %, 1.9 wt. %, and 2.0 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer present in the topical composition are contemplated within the scope of the invention.

[0033] In some embodiments, the topical compositions comprises disodium EDTA in any amount up to its solubility limit. In some embodiments, the amount of disodium EDTA in the topical composition may be, for example, at least 0.01 wt. %, at least 0.05 wt. %, at least 0.10 wt. %, at least 0.15 wt. %, at least 0.20 wt. %, or within a range defined by any two of the aforementioned concentrations. Approximately 0.05 wt. %, 0.06 wt. %, 0.07 wt. %, 0.08 wt. %, 0.09 wt. %, 0.10 wt. %, 0.11 wt. %, 0.12 wt. %, 0.13 wt. %, 0.14 wt. %, and 0.15 wt. % disodium EDTA present in the topical composition are contemplated within the scope of the invention.

[0034] In some embodiments, the topical compositions comprises water in a quantity sufficient such that the all of the components of the topical composition add to 100 percent.

[0035] In some embodiments the topical composition may comprise a 1:2 mass ratio of L-arginine to L-citrulline

[0036] In some embodiments the topical composition may comprise a mass ratio of 72:9:6:4:8 of sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline, respectively.

[0037] In some embodiments, the topical composition provided herein may comprise a pharmaceutical carrier, diluent, co-solvent, emulsifier, penetration enhancer, preservative, emollient, or a combination thereof. Acceptable carriers or diluents for therapeutic use are well-known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, 18th Ed., Mack Publishing Co., Easton, PA (1990), which is incorporated herein by reference in its entirety.

[0038] Preservatives, stabilizers, dyes, fragrances, and the like may be provided in the topical composition. For example, sodium benzoate, ascorbic acid, benzyl benzoate, and esters of p-hydroxybenzoic acid may be added as preservatives. In addition, antioxidants and suspending agents may be used. In one or more of the comtemplated embodiments, alcohols, esters, sulfated aliphatic alcohols, and the like may be used as surface active agents; cellulose acetate phthalate as a derivative of a carbohydrate such as cellulose or sugar, or methylacetate-methacrylate copolymer as a derivative of polyvinyl may be used as suspension agents; and plasticizers such as ester phthalates and the like may be used as suspension agents.

[0039] In certain embodiments, the topical composition may comprise sorbitol, isopropyl alcohol, propylene glycol, butylated hydroxytoluene, triethanolamine, benzyl alcohol, benzyl benzolate, PEG 40-hydrogenated castor oil, acrylate/C_{10-30} alkyl acrylate crosspolymer, disodium EDTA, or water; or a combination thereof.

[0040] In other embodiments, provided herein is a method for improving the sensitivity of the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0041] In some embodiments, provided herein is a method for improving blood flow to the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0042] In some embodiments, provided herein is a method for improving the symptoms of neuropathy comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline. In some embodiments, provided herein is a method for providing at least partial relief of at least one of the symptom of neuropathy comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline. In a preferred embodiment, the neuropathy is diabetic neuropathy.

[0043] In some embodiments, provided herein is a method for improving blood flow to the skin and improving sensitivity of the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0044] In some embodiments, provided herein is a method for improving blood flow to the skin and improving the symptoms of diabetic neuropathy comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0045] In some embodiments, provided herein is a method for improving sensitivity of the skin and improving the symptoms of diabetic neuropathy comprising

applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0046] In some embodiments, provided herein is a method for improving blood flow to the skin, improving sensitivity of the skin, and improving the symptoms of diabetic neuropathy comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline.

[0047] In certain embodiments, the topical compositions provided herein are intended for topical, non-invasive, application to the genital regions, especially the penis, its entirety, or preferably just the glans of the penis. In addition, the composition may be applied to the scrotum and/or perineum. One particular advantage of the compositions provided herein is that the compositions are effective even when applied to only the glans penis.

[0048] In certain embodiments, the topical composition may be applied to the skin of the human penis in order to improve sensitivity. In some embodiments, the topical composition may be applied to the skin of the human penis to improve blood flow. In some embodiments, the topical composition may be applied to a circumcised human penis to improve sensitivity. In some embodiments, the topical composition may be applied to a circumcised human penis to blood flow. In some embodiments, the topical composition may be applied to the skin of an uncircumcised human penis to improve sensitivity. In some embodiments, the topical composition may be applied to the skin of an uncircumcised human penis to improve blood flow.

[0049] For increasing sensitivity of the penis during sexual activity, and with the preferred application on the glans penis, the amount of formulation to be applied is preferably in the range of from about 10 to about 1000, from about 50 to about 500, from about 100 to about 400, or from about 150 to about 300 mg per application, or may be within a range defined by any of two of the aforementioned amounts per application.

[0050] In some embodiments, the composition is administered 1 to 4 times per day, preferably 2 times a day. In some embodiments, the compounds will be administered for a period of continuous therapy, for example for one day, two days, three days, a week, two weeks, one month, or more, or for months or years.

[0051] The terms “pharmaceutically acceptable carrier” and “pharmaceutically acceptable excipient,” as used herein, include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. In addition, various adjuvants such as are commonly used in the art may be included. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman’s: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press, which is incorporated herein by reference in its entirety.

[0052] The term “excipient,” as used herein, refers to an inert or relatively inert substance that is added to a pharmaceutical composition to impart certain properties to the composition including, without limitation, improved or desired bulk, consistency, stability, binding ability, lubrication, disintegrating ability, etc.. A “diluent” is a type of excipient.

EXAMPLE 1

[0053] Materials used in preparing the topical sensitization cream described herein may be made by known methods or are commercially available. It is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. The skilled artisan given the literature and this disclosure is well equipped to prepare the formulations of the instant application.

[0054] Representative topical formulations according to the invention are shown in Table 1 below, with the amounts for "broad", "intermediate" and "preferred" ranges.

TABLE 1: Representative Topical Compositions

Component	Broader Range wt. %	Narrower Range wt. %
sweet almond oil[1]	3.0-10.0	5.0-7.0
cinnamon bark oil[2]	0.1-2.0	0.5-1.25
coriander seed oil[3]	0.1-1.0	0.25-0.75

L-arginine	0.05-5.0	0.2-0.6
L-citrulline	0.1-8.0	0.4-0.8
sorbitol solution USP 70%	1.0-10.0	3.0-7.0
isopropyl alcohol USP 70%	1.0-10.0	2.0-6.0
propylene glycol	10.0-30.0	15.0-25.0
butylated hydroxytoluene	0.1-3.0	0.5-1.5
triethanolamine	0.1-3.0	0.5-1.5
benzyl alcohol	0.1-3.0	0.5-1.5
benzyl benzolate	0.1-3.0	0.5-1.5
PEG 40-hydrogenated castor oil	1.5-5.5	2.5-4.5
acrylate/C_{10-30} alkyl acrylate crosspolymer	0.5-2.0	1.0-1.6
disodium EDTA	0.01-0.20	0.05-0.15
water	40.0-60.0	50.0-56.0

[1] *Prunus Amygdalus Dulcis* oil; [2] *Cinnamomum Zeylanicum* bark oil; [3] *Coriandrum Sativum* seed oil

EXAMPLE 2

EFFECT OF COMPOSITION ON BLOOD FLOW

[0055] A total of 36 CD-1 mice (Taconic Farms) aged 6 to 8 weeks were randomized according to their weights into three groups: Mice in Group 1 were left untreated to serve as a control group; mice in Group 2 received a placebo composition; and mice in Group 3 received the treatment composition. Mice were dosed with the treatmentcomposition or placebo by applying 0.1 mL of the composition directly to the tail. The mice were treated three times a day for 14 days, with treatment commencing on day 1.

[0056] The mice were acutely anesthetized with isoflurane (approximately 2%-3.5% at 1L/min for all measurements. All blood flow measurements were made with a MoorLab laser Doppler (Moor Instruments) perfusion monitor with an appropriately sized Doppler probe and calibrated with the "Probe Flux" standard. Blood flow was measured on days 0, 7, and 14 at a consistent site on the tail identified with a permanent marker. The Doppler probe was place just above the tail capillary but not in contact with the tail tissue.

Figure 1 shows a statistically significant increase in blood flow in the tails of mice treated with the test composition as compared with either place-treated or untreated mice.

EXAMPLE 3

EFFECT OF COMPOSITION ON TOPICAL PAIN

[0057] A total of 30 CD-1 mice (Taconic Farms) aged 6 to 8 weeks were randomized into two groups: Mice in Group 1 were treated with a placebo composition and mice in Group 2 were treated with treatment composition. Mice were dosed with the treatment composition or placebo by applying 0.1 mL of the composition directly to the tail. The mice were treated three times a day for 14 days, with treatment commencing on day 1.

[0058] The tail flick time (i.e. the time it takes for the mouse's tail to flick after being placed on a hot plate) was measured at day 1 and day 14. Figure 2 shows a statistically significant increase in tail flick time of mice treated with the test composition as compared with placebo-treated mice.

[0059] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A method for improving the sensitivity of the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion.

2. The method of Claim 1, wherein the composition is applied to the skin.

3. The method of Claim 2, wherein the skin is on the foot or hand.

4. The method of Claim 3, wherein the skin is on the penis.

5. The method of Claim 4, wherein the penis is circumcised or uncircumcised.

6. The method of any one of Claims 1 to 5, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 wt. % cinnamon bark oil, about 0.5 wt. % coriander seed oil, about from about 0.33 wt. % to about 3.0 wt. % L-arginine, and from about 0.67 wt. % to about 6.0 wt. % L-citrulline.

7. The method of any one of Claims 1 to 5, wherein the mass ratio of L-arginine to L-citrulline is about 1:2.

8. The method of any one of Claims 1 to 5, wherein the mass ratio of sweet almond oil to cinnamon bark oil to coriander seed oil to L-arginine to L-citrulline is about 72:9:6:4:8.

9. The method of any one of Claims 1 to 5, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 weight percent cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, from about 0.68 to about 6.0 wt. % L-citrulline, about 5.0 wt. % of a 70 percent by weight sorbitol solution in water, about 4.0 wt. % of a 70 percent by weight isopropyl alcohol solution in water, about 20.0 wt. % propylene glycol, about 1.0 wt. % butylated hydroxytoluene, about 1.0 wt. % triethanolamine, about 1.0 wt. % benzyl alcohol, about 1.0 wt. % benzyl benzoate, about 3.5 wt. % PEG 40-hydrogenated castor oil, about 1.3 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer, about 0.1 wt. % ethylenediaminetetraacetic acid disodium salt, and the balance water.

10. The method of any of Claims 1 to 5, wherein a dose of about 0.5 mL to about 5 mL of the composition is applied to the skin from two to three times daily for a period of from two to three weeks, and from once to twice daily as needed thereafter.

11. A method for improving blood flow to the skin comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion.

12. The method of Claim 11, wherein the composition is applied to the skin.

13. The method of Claim 12, wherein the skin is on the foot or hand.

14. The method of Claim 11 wherein the skin is on the penis.

15. The method of Claim 14, wherein the penis is circumcised or uncircumcised.

16. The method of any one of Claims 11 to 15, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 wt. % cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, and from about 0.68 to about 6.0 wt. % L-citrulline.

17. The method of any one of Claims 11 to 15, wherein the mass ratio of L-arginine to L-citrulline is about 1:2.

18. The method of any one of Claims 11to 15, wherein the mass ratio of sweet almond oil to cinnamon bark oil to coriander seed oil to L-arginine to L-citrulline is about 72:9:6:4:8.

19. The method of any one of Claims 11 to 15, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 weight percent cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, from about 0.68 to about 6.0 wt. % L-citrulline, about 5.0 wt. % of a 70 percent by weight sorbitol solution in water, about 4.0 wt. % of a 70 percent by weight isopropyl alcohol solution in water, about 20.0 wt. % propylene glycol, about 1.0 wt. % butylated hydroxytoluene, about 1.0 wt. % triethanolamine, about 1.0 wt. % benzyl alcohol, about 1.0 wt. % benzyl benzoate, about 3.5 wt. % PEG 40-hydrogenated castor oil, about 1.3 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer, about 0.1 wt. % ethylenediaminetetraacetic acid disodium salt, and the balance water.

20. The method of any of Claims 11 to 15, wherein a dose of from about 0.5 mL to about 5 mL of the composition is applied to the skin from two to three times daily for a period of from two to three weeks and from once to twice daily as needed thereafter.

21. A method for treating neuropathy comprising applying to the skin an effective amount of a topical composition comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion.

22. The method of Claim 21, wherein the composition is applied to the skin.

23. The method of Claim 22, wherein the skin is on the feet or hands.

24. Tis applied to the skin from two to three times daily for a period of from two to three weeks and from once to twice daily as needed thereafter.

25. The method of Claim 24, wherein the penis is circumcised or uncircumcised.

26. The method of any one of Claims 21 to 24, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 wt. % cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, and from about 0.68 to about 6.0 wt. % L-citrulline.

27. The method of any one of Claims 21to 24, wherein the mass ratio of L-arginine to L-citrulline is about 1:2.

28. The method of any one of Claims 21 to 24, wherein the mass ratio of sweet almond oil to cinnamon bark oil to coriander seed oil to L-arginine to L-citrulline is about 72:9:6:4:8.

29. The method of any one of Claims 21 to 24, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 weight percent cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 wt. to about 3.0 % L-arginine, from about 0.68 to about 6.0 wt. % L-citrulline, about 5.0 wt. % of a 70 percent by weight sorbitol solution in water, about 4.0 wt. % of a 70 percent by weight isopropyl alcohol solution in water, about 20.0 wt. % propylene glycol, about 1.0 wt. % butylated hydroxytoluene, about 1.0 wt. % triethanolamine, about 1.0 wt. % benzyl alcohol, about 1.0 wt. % benzyl benzoate, about 3.5 wt. % PEG 40-hydrogenated castor oil, about 1.3 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer, about 0.1 wt. % ethylenediaminetetraacetic acid disodium salt, and the balance water.

30. The method of any of Claims 21 to 29, wherein the dose of 0.5 to 5 mL of the composition are applied to the skin two to three times daily for a period of two to three weeks and once to twice daily as needed thereafter.

31. The method of any of Claims 21 to 30, wherein the neuropathy is diabetic neuropathy.

32. A topical composition for improving blood flow to the skin and the sensitivity of the skin comprising sweet almond oil, cinnamon bark oil, coriander seed oil, L-arginine, and L-citrulline in an oil-in-water emulsion.

33. The composition of Claim 33, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 wt. % cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, and from about 0.68 to about 6.0 wt. % L-citrulline.

34. The composition of any one of Claims 32 to 33, wherein the mass ratio of L-arginine to L-citrulline is approximately 1:2.

35. The composition of any one of Claims 32 to 33, wherein the mass ratio of sweet almond oil to cinnamon bark oil to coriander seed oil to L-arginine to L-citrulline is about 72:9:6:4:8.

36. The composition of any one of Claims 32 to 33, further comprising one or more pharmaceutically acceptable excipients.

37. The composition of any one of Claims 32 to 33, wherein the composition comprises: about 6 wt. % sweet almond oil, about 0.75 weight percent cinnamon bark oil, about 0.5 wt. % coriander seed oil, from about 0.34 to about 3.0 wt. % L-arginine, from about 0.68 to about 6.0 wt. % L-citrulline, about 5.0 wt. % of a 70 percent by weight sorbitol solution in water, about 4.0 wt. % of a 70 percent by weight isopropyl alcohol solution in water, about 20.0 wt. % propylene glycol, about 1.0 wt. % butylated hydroxytoluene, about 1.0 wt. % triethanolamine, about 1.0 wt. % benzyl alcohol, about 1.0 wt. % benzyl benzoate, about 3.5 wt. % PEG 40-hydrogenated castor oil, about 1.3 wt. % acrylate/C_{10-30} alkyl acrylate crosspolymer, about 0.1 wt. % ethylenediaminetetraacetic acid disodium salt, and the balance water.

38. The composition of any one of Claims 26 to 27, wherein the composition comprises from about 150 mg to about 3.0 g L-arginine and from about 300 to about 3.0 g L-citrulline.

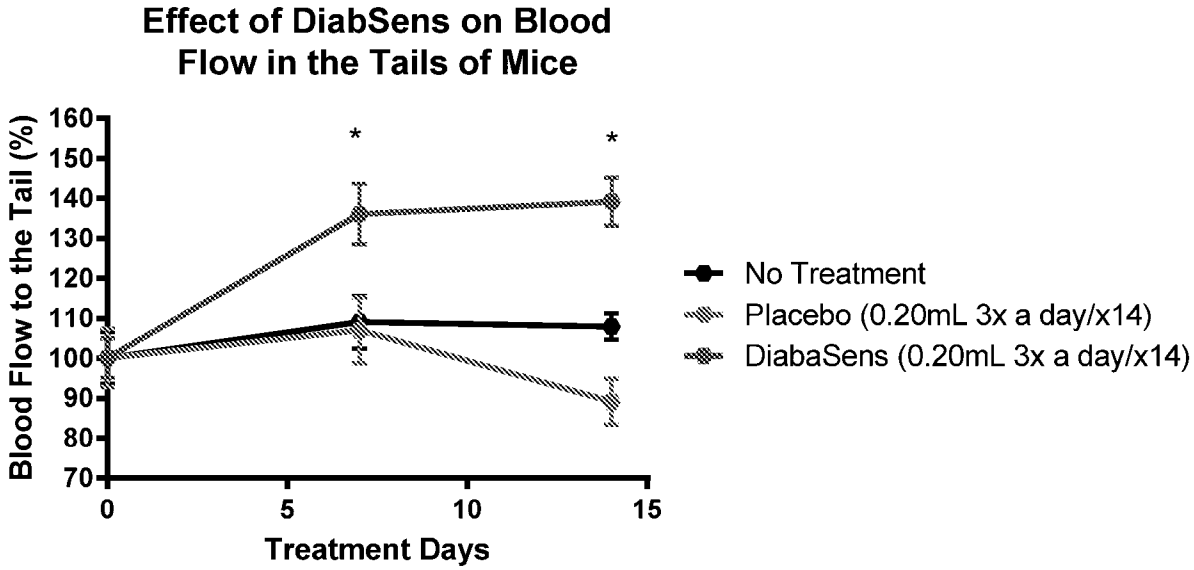

Effect of DiabSens on Blood Flow in the Tails of Mice
Blood Flow to the Tail (%)
160
150
140
130
120
110
100
90
80
70
0
5
10
15
Treatment Days
*
*
No Treatment
Placebo (0.20mL 3x a day/x14)
DiabaSens (0.20mL 3x a day/x14)

FIGURE 1

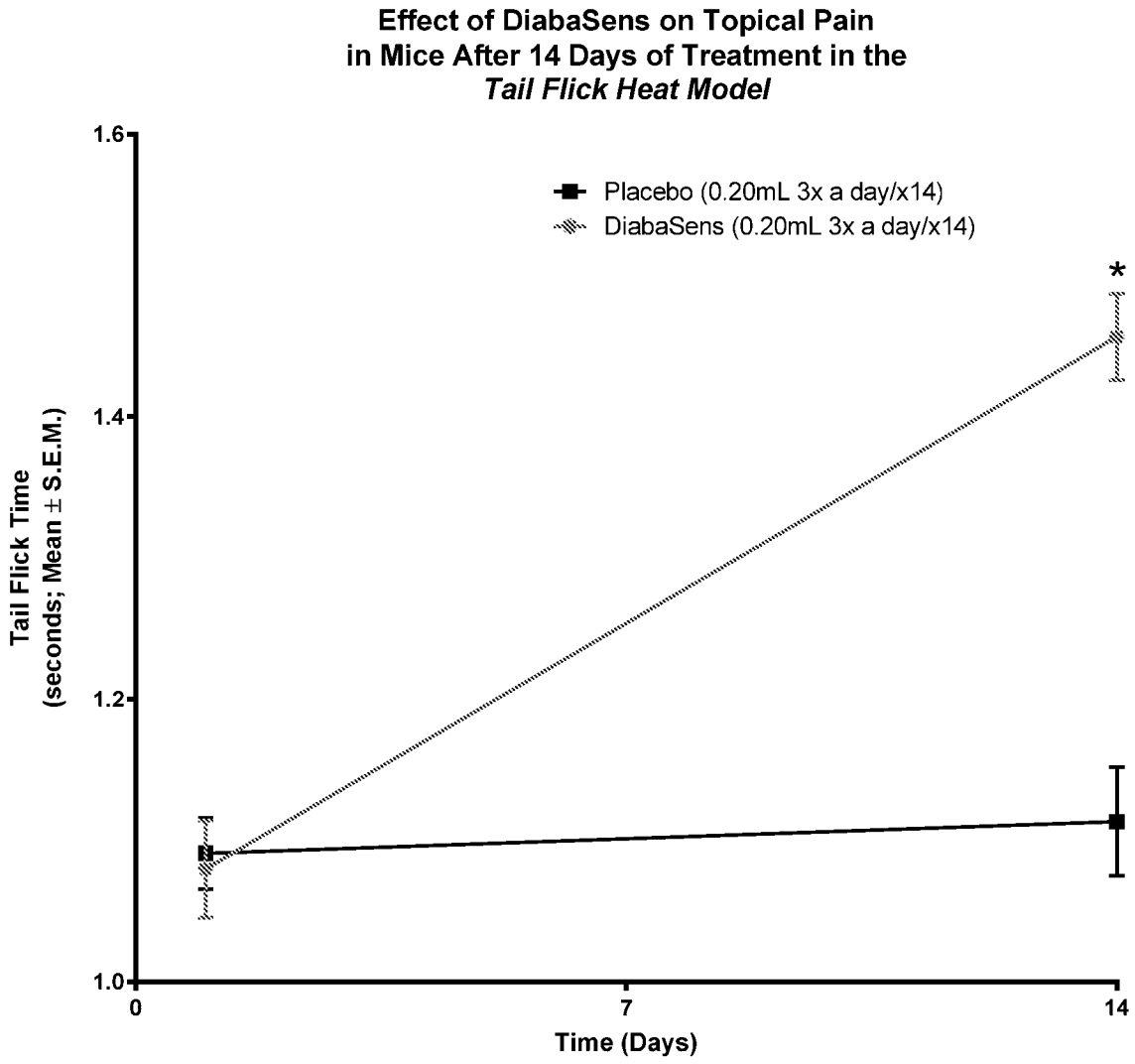

Effect of DiabaSens on Topical Pain
in Mice After 14 Days of Treatment in the
Tail Flick Heat Model
Placebo (0.20mL 3x a day/x14)
DiabaSens (0.20mL 3x a day/x14)
*
Tail Flick Time
(seconds; Mean ± S.E.M.)
1.6
1.4
1.2
1.0
0
7
14
Time (Days)

FIGURE 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/17024

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C09K 3/00 (2019.01)
CPC - A61Q 19/00, A61K 36/23, A61K 9/107, Y10S 514/887, A61K 8/062

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)
See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y --- A	US 2015/0110904 A1 (CENTRIC RESEARCH INSTITUTE) 23 April 2015 (23.04.2015) para [0002], [0005]-[0006]	1-8, 10-18, 20-28 and 32-36 --- 9, 19, 29 and 37
Y --- A	US 2013/0164394 A1 (FERRARI et al.) 27 June 2013 (27.06.2013) para [0001], [0007]-[0008], [0022]-[0023], [0046], [0048], [0071], [0175]-[0179]; example 3	1-8, 10-18, 20, 25 and 32-36 --- 9, 19 and 37
Y ----- A	US 2008/0193385 A1 (MAIBACH) 14 August 2008 (14.08.2008) para [0003]-[0004], [0007]-[0008], [0051], [0068]; abstract	3-5, 13, 21-24 and 26-28 --- 29
A	US 2015/0217019 A1 (JEANNETTE MARTELLO) 6 August 2015 (06.08.2015) para [0051], [0059], [0066], [0068], [0074], [0079], [0111]; abstract	9, 19, 29 and 37
A	US 2015/0342854 A1 (HAYASHIBARA CO., LTD.) 3 December 2015 (03.12.2015) para [0025], [0027], [0068]-[0069], [0071], [0075], [0078], [0081], [0117], [0130]; abstract	9, 19, 29 and 37
A	US 2009/0324658 A1 (NOHATA et al.) 31 December 2009 (31.12.2009); the entire document	1-29 and 32-37

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2019	25 APR 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/17024

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

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

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

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

3. ☒ Claims Nos.: 30-31 and 38
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

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

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.