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(54) Title: NASAL SPRAY FORMULATION

(57) Abstract: The present invention relates to a formulation used as a nasal spray containing nigella oil. The present invention particularly relates to a non-sterile formulation with natural content comprising nigella sativa oil aimed to be applied to the nasal mucosa for moisturizing the nasal mucosa and eliminating nasal congestion, that provides a protective barrier and reduces mucosal irritation, inflammation, edema and allergic rhinitis.



NASAL SPRAY FORMULATION

Technical Field of the Invention

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The present invention relates to a formulation used as a nasal spray containing nigella oil.

The present invention relates to a non-sterile formulation with natural content comprising nigella sativa oil aimed to be applied to the nasal mucosa for moisturizing the nasal mucosa and eliminating nasal congestion, that provides a protective barrier and reduces mucosal irritation, inflammation, edema and allergic rhinitis.

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State of the Art

Majority of human beings prefer to breathe through their noses. Breathing through the nose is essential for aerating auditory canal, for proper functioning of both olfactory and gustatory senses, as well as for moisturizing and heating the air. Nasal mucosa and nasal conchae assume an important role in moisturizing, heating and cleaning by filtering the air breathed through the nose. Thus, nose can generate air that is healthier for both our throat and for our lungs, thereby allowing them to function and helping in providing oxygen to the body. A congested nose means a body which is partially deprived of these functions.

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Nasal congestion is the blockage occurring in nasal passageways which emanates from swelling of nose, adjacent tissues and blood vessels with excessive volume of fluids. Rheum, also known as nasal discharge may or may not be observed together with nasal congestion. This problem may originate from any condition causing irritation on nasal tissues or inflammation. Infection, cold weather, allergens, air conditioning and ventilation systems are among the primary reasons causing this problem.

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Nasal congestion which frequently observed in otolaryngologic diseases as well as during seasonal changes is a problem that substantially affects the quality of life of human beings. Being unable to breathe freely may result in nasal and post-nasal drip, headache, snoring,

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morning fatigue, chronic fatigue and performance decrease during the day. As aforementioned problem may also inhibit hearing and speaking, it may also cause disorders such as ageusia and anosmia as well as frequently recurring throat infections.

5 In cases where nasal congestion is present, the first method implemented to solve this problem is using nasal decongestants or sprays. Many of the commercially available nasal sprays function by inducing vasoconstriction, thereby reducing the volume therein. Thus, once the blood flow rate has decreased, blood cells causing edema cannot reach respective region, thereby ameliorating edema. Said nasal sprays which should be limited to short-term
10 use, manifest severe side-effects including disrupting inflation-deflation cycle, causing addiction as well as damage in the nasal tissues and inducing chronic nasal congestions in case of long-term use. Furthermore, they also induce mild side-effects such as stinging, burning and dryness sensation during use. Process integrity for filtering, cleaning of the nasal mucosa may be disrupted with the damage caused to the mucosal structure. The use of
15 nasal sprays of this type is also limited in patients with systemic diseases such as hypertension and glaucoma. Moreover, cartilage tissue may become affected and damage may be observed in septums in case of long-term use.

Active ingredients of oxymetazoline and xylometazoline are either used individually or in
20 combination in commercially available nasal sprays for the treatment of nasal congestion. US patent application numbered US2006222718 relates to a stable aqueous solution prepared by using a combination of aforementioned agents and used for eliminating nasal congestions. Said application discloses a formulation that aims to improve the stability of active ingredients by using a zinc salt and a buffer salt and reduce side-effects stemming
25 from undesired substances emerging due to degradation.

US patent application numbered US6599883B1 relates to the use of nasal sprays containing xylitol for the treatment of upper respiratory infections and otitis. Xylitol produces desired effects by means of inhibiting and/or reducing growth and acid release of certain bacteria
30 such as *S. Mutans* and *Streptococcus pneumonia*. US patent document numbered US 2014/0228304 A1 which belongs to the same applicant relates to the use of xylitol in combination with anti-mucosal compositions. It is stated that xylitol, as used in these combinations, alleviates side-effects such as dryness caused by anti-mucosal compositions.

Effects of nasal administration of nigella sativa oil and isotonic sodium chloride solution were compared in literature in terms of relieving nasal symptoms of old aged adults (Cagatay Oysu vd. (2014), Topical Nigella Sativa for nasal symptoms in elderly. *Auris Nasus Larynx*, 41 269-272). Said study mentions that in addition to dryness in nasal mucosa, cold and dry weather conditions also result in issues including burning, itching and nasal congestion, and that these symptoms manifest themselves in air-conditioned environments particularly in long flights where humidity levels are low. It is indicated that adults of old age are affected even more by the aforementioned negative conditions. The first treatment referred for relieving these symptoms is the nasal administration of isotonic sodium chloride solution. Alternatively, the use of sesame seed oil that contains tocopherol which is capable of neutralizing ozone and nitrous oxides present in the air inhaled, and of preventing both tissue damage and inflammation is also well-known. Although there are numerous studies indicating that nigella sativa oil which contains as much tocopherol as sesame seed oil does, provides significant reduction in symptoms of both allergic rhinitis and asthma when administered orally, it is stated that there are no studies discussing the topical administration of nigella sativa oil. In the study, isotonic sodium chloride solution and nigella sativa oil were administered separately to geriatric patients for a period of 2 weeks. There is a washout period of 3 weeks between aforementioned administration periods. Subjective symptoms including intranasal burning, congestion, itching and scabbing were evaluated on a visual analog scale and with a mucociliary function saccharine test. No significant differences were observed between the nasal use of both nigella sativa oil and isotonic saline solution for intranasal burning and itching symptoms at the end of the study period. Moreover, no changes were observed in terms of mucociliary clearance during any of said treatment periods. In contrast thereof, patients' symptoms of intranasal dryness, congestion and scabbing in geriatric group treated with nigella sativa oil showed significant relief when compared to patients who were administered isotonic saline solution.

Another study reported in the literature relates to the topical administration of nigella sativa oil in the treatment of allergic rhinitis (Abdulghani Mohamed Alsamarai vd. (2014) Evaluation of Topical Black Seed Oil in the Treatment of Allergic Rhinitis. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, 13, 75-82). Allergic rhinitis is chronic inflammatory disease which may be observed at any age, however, usually encountered in childhood and adolescence.

Said study reported that there is no method for the treatment of this disease and many of the administered medications provide symptomatic relief. Furthermore, these medications may

manifest side effects and further result in withdrawal symptoms. The aim of this study was to evaluate the therapeutic efficacy of nigella sativa extract for nasal administration in the treatment of allergic rhinitis. A total of 68 patients who suffered from allergic rhinitis were included in the study. 19 out of 68 patients had mild symptoms, 28 out of 68 patients had moderate symptoms, whereas 21 out of 68 patients had severe symptoms. Each group was divided into active and control subgroups. A skin test was administered in order to ensure that patients' symptoms were indeed allergy-derived and patients who produced negative results were excluded from the study. Patients included in the active group were treated with nigella sativa oil, while patients included in the control group were administered conventional cooking oil in the form of nasal drops for a period of 6 weeks. Subsequent to the 6-week treatment period, 100% of the patients with mild symptoms and who were included in the active group had complete symptom relief, 68.7% of the patients with moderate symptoms and who were included in the active group had complete relief of symptoms, while 25% of which showed alleviated symptoms, whereas, 58.3% of the patients with severe symptoms and who were included in the active group had complete symptom relief, while 25% of which had alleviated symptoms. 92.1% of the total of patients included in the active group had full symptom relief or alleviated symptoms, while the rate for the control group remained at 30.1%. At the end of the 6-week treatment period, tolerance for allergen exposure in the active group improved through topical administration and the rate was 55.5%. This data is determined to be statistically significant when compared to 20% rate established in the control group ($P=0.006$). In conclusion thereof, said study indicated that nigella sativa oil is determined to be effective in the treatment of allergic rhinitis, that the topical administration of said oil is more effective and causes less side effects when compared to oral administration.

There is clearly a need for developing novel formulations in order to eliminate disadvantages and shortcomings experienced in the state of the art and disclosed above.

The present application seeks to solve problems encountered in the state of the art. The inventive formulation disclosed in the present application allows for cleaning the upper respiratory tract, thereby removing microorganisms, allergens and irritants which may be potentially harmful to ear, nose and throat. Moreover, it further moisturizes and relieves the nose in nasal congestion, dryness and irritations stemming from dry weather, influenza, common cold and allergy by means of the moisturizing characteristics of essential oils present in its content.

Objects of the Invention

It is therefore an object of the present invention to provide a formulation with intranasal administration for the prevention and/or treatment of nasal congestion, nasal dryness and irritation.

It is thus another object of the present invention to provide a formulation with intranasal administration for relieving symptoms of allergic rhinitis.

It is thus another object of the present invention to provide a formulation that creates a protective barrier and alleviates mucosal irritation, inflammation and edema without producing pharmacological, immunological or metabolic effects.

It is therefore another object of the present invention to minimize side effects that affect human health adversely by means of preparing a mixture with natural content and without incorporating any preservatives or additives, and to obtain a formulation that is both non-addicting and suitable for long-term use.

Detailed Description of the Invention

The present invention relates to a nasal spray for decongesting nasal obstructions and moisturizing nasal mucosa, that eliminates aforementioned disadvantages and meets respective requirements.

A dry or congested nose cannot perform respiratory functions adequately. Accordingly, fluid of nasal mucosa may carry germs to ears, nose and throat. Since the inventive formulation will clear and decongests sinuses and nasal tracts once it is administered, it will accordingly remove microorganisms, allergens and irritants that may potentially be harmful to ears, nose and throat, and discharge them from the nose. The inventive formulation moisturizes and relieves the nose in nasal dryness and irritation cases which are caused either by dry air generated by air conditioners, ventilation systems and weather conditions or by influenza,

common cold and allergies since it serves as a natural moisturizer by means of the essential oils present in its content. The inventive formulation further helps relieving the symptoms of allergic rhinitis by means of therapeutic effect of nigella sativa oil contained therein.

The inventive formulation is formed from a mixture of purified water, nigella sativa oil, salt (NaCl), xylitol, xanthan gum, eucalyptus oil, peppermint oil and grapefruit seed extract. Active ingredients of eucalyptus and peppermint oils included in the inventive formulation are commonly used in formulations for decongesting nasal obstructions and alleviating allergic symptoms due to their potent decongestive effects. Xylitol is added to compositions in order to prevent nasal dryness caused by active ingredients particularly included in anti-mucosal compositions. Nigella sativa oil which is one of the active ingredients included in the inventive formulation has a therapeutic potential in the treatment of respiratory tract diseases due to its anti-inflammatory, anti-oxidant, anti-histaminic, anti-microbial and analgesic effects. Therapeutic effect of nigella sativa oil originates from tocopherol that neutralizes ozone and nitrous oxides present in the air inhaled and inhibits tissue damage and inflammation as well as from four different active ingredients (thymoquinone, carvacrol, tanetol and 4-terpineol) which are capable of neutralizing free radicals. Nigella sativa oil may inhibit the inflammation of sinuses and respiratory tracts and prevent microbial infections by means of the ingredients present in its content, thereby alleviating clinical symptoms of upper respiratory tract infections including nasal congestion, head, neck and earache as well as the symptoms of allergic rhinitis.

Components included in the inventive formula, functions and amounts in percentage thereof are presented in the following table:

Component	Function	Amount (%)
Purified Water	Excipient	0.1-99.9
Nigella Sativa Oil	Active Ingredient	0.1-99.9
Salt (NaCl)	Excipient	0.01-20.0
Xylitol	Active Ingredient	0.01-15.0
Emulgator (Xanthan Gum)	Thickener	0-5
Eucalyptus Oil	Active Ingredient	0.001-1.0

Peppermint Oil	Active Ingredient	0.001-1.0
Preservative (Grapefruit Seed Extract)	Natural Microbial Preservative	0-6

Substances used in the inventive formula are commercially available.

- 5 Substances are weighed in order to ensure that they are provided in determined amounts for preparing the formulation and mixed at room temperature. Obtained mixture is preserved inside tightly closed and dark-colored bottles below the room temperature (25°C).

10 Nasal spray may be administered either by spraying or dropping 1-2 times to each nasal mucosa as frequent as desired within a day.

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CLAIMS

1. A nasal spray formulation containing nigella sativa oil for using in the treatment of nasal dryness, nasal congestion and allergic rhinitis symptoms stemming from dry air or influenza or common cold **characterized in that**, it comprises; purified water, nigella sativa oil, salt (NaCl), xylitol, eucalyptus oil, peppermint oil, emulgator and microbial preservative.
2. Nasal spray formulation according to Claim 1 **characterized in that**, it comprises the following by weight in the entire formulation;
- (a) purified water approximately in a range between 0.01% and 99.9%
 - (b) nigella sativa oil approximately in a range between 0.01% and 99.9%
 - (c) salt (NaCl) approximately in a range between 0.01% and 20%
 - (d) xylitol approximately in a range between 0.01% and 15%
 - (e) emulgator approximately in a range between 0% and 5%
 - (f) eucalyptus oil approximately in a range between 0.01% and 1%
 - (g) peppermint oil approximately in a range between 0.01% and 1%
 - (h) microbial preservative approximately in a range between 0% and 6%.
3. Nasal spray formulation according to Claim 1 **characterized in that**, said emulgator is xanthan gum and/or rosemary extract and/or mallow extract and/or lemon seed extract.
4. Nasal spray formulation according to Claim 1 **characterized in that**, said microbial preservative is preferably grapefruit seed extract.
5. Nasal spray formulation according to Claim 1 **characterized in that**, it is administered to nasal mucosa either by spraying or dropping.