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(57) Abrégé/Abstract:
The present invention relates to a product comprising capsaicin or a capsaicinoid for use in the treatment of cough, in particular chronic persistent unexplained cough or increased cough reflex sensitivity. More precisely, the present invention concerns oral formulations for reducing and relieving coughing from other irritants than capsaicin itself. The capsaicin formulations are stated to down-regulate coughing following a regular consumption. Said products can also be used in the treatment of rhinitis and other conditions known to have cough symptoms.

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COUGH REDUCING PRODUCT

Field of the Invention

The present invention relates generally to a product for use in the treatment of cough and the use of the product for the preparation of a compositions for the treatment of cough and cough reduction caused by various irritants. The invention also relates to the use of the composition for treating cough.

Description of the related art

Cough is an essential protective physiological mechanism to prevent food and liquid, dust, and chemicals to reach the lower airways, but it is also a symptom of many inflammatory diseases of the lungs. Coughing is one of the most common symptoms for which patients consult a doctor in the western world and current therapies are often unsatisfactory [1,2]. Chronic cough is also clearly associated with significant social and psychological impacts[3,4]. Patients with cough without any obvious explanation to the problem are often seen in clinical care and cough is arbitrarily defined as being chronic when it has lasted for more than 8 weeks [5], even if the definition of chronic cough varies in the literature. Epidemiologic studies indicate that chronic cough is very prevalent in the community (up to 20% of the population) and could be increasing in relation to rising environmental pollution [2]. In the present application such patients will be referred to as having chronic persistent unexplained cough. How common this condition is has also been debated [5,6]. However, since there still are patients with cough for which no cure has been found, there is a need for a product (medicament) which may be used for treatment of cough and reduce or relieve coughing, e.g. to be used in treatment of patients having chronic persistent unexplained cough or increased cough reflex sensitivity.

Summary of the invention

The invention relates to a food additive, pharmaceutical preparation or the like for oral intake, for example formulated as a tablet, capsule, powder, syrup, drink or other suitable formulations that comprises capsaicin, the “hot” ingredient in chili pepper. More precisely the invention concerns a new application of orally taken capsaicin to relive and reduce coughing and rhinitis caused by other irritants then the capsaicin itself. We believe that we for the first

time disclose the idea of using oral intake of low doses of capsaicin to ameliorate irritation based cough and rhinitis from other irritants then capsaicin.

The idea to use capsaicin as an active substance for treatment of cough is based on an extensive work in finding a treatment for cough. Since cough is a commonly occurring symptom around the world, a lot of efforts have been done in identifying causes and possible cures. When known causes for cough such as various infections, cancer, foreign body aspiration, cystic fibrosis, alveolitis, asthma, chronic obstructive pulmonary disease (COPD), medication with angiotensin converting enzyme (ACE) inhibitor, gastroesophageal reflux disease (GERD) or post-nasal drip syndrome have been excluded, still a group of patients with unexplained cough remains. A discrete clinical entity has been suggested for patients with such chronic cough in whom the cough is often triggered by environmental stimuli and, furthermore, in whom it initially may have developed after an upper respiratory tract infection [7]. A similar group of patients with airway symptoms induced by environmental irritants report problems with coughing, chest discomfort, dyspnoea, rhinitis and eye irritation has been identified [8,9]. The symptoms mimic asthma, but asthma-specific tests are negative. These patients have an increased cough reaction to inhaled capsaicin (the active compound of chili peppers), CAS nr 404-86-4, a tasteless and odorless substance that stimulates sensory nerves and reflects sensory nerve reactivity [10]. Such airway symptoms are interpreted as airway sensory hyperreactivity (SHR). Cigarette smoke, car exhaust and perfumed products are some of the triggers for SHR symptoms [8]. In most cases, these patients could also be diagnosed with chronic persistent unexplained cough [6] or cough hypersensitivity syndrome [11]. SHR affects more than 6% of the adult population in Sweden, mainly women, according to a population-based epidemiologic study [12] where SHR diagnosis was based on a questionnaire, the chemical sensitivity scale for sensory hyperreactivity (CSS-SHR), in combination with a standardized positive capsaicin inhalation provocation test [13,14].

Morice et al. have developed a questionnaire; the Hull Airway Reflux Questionnaire (HARQ) to identify coughers with a novel paradigm for understanding chronic cough [15]. This paradigm; the "Cough Hypersensitivity Syndrome" includes as well patients with symptoms that may indicate a reflux disease as patients with a general hypersensitivity towards e.g. environmental irritants. The patients are classified as having a cough hypersensitivity syndrome that also comprises both sensitivity to environmental irritants and augmented capsaicin cough answer [11,16].

In recent years there has been an emerging interest in the family of transient receptor

potential (TRP) ion channels, which can be found in most of the human organ systems. They are able to sense temperature, noxious stimuli, pain, stretch, and osmolarity, among other factors. The main foci of such triggers in the airways are ion channels belonging to the transient receptor potential vanilloid (TRPV) and the transient receptor potential ankyrin (TRPA) families [17-20]. The first genetically identified TRP receptor was the TRPV1, also called the capsaicin receptor, as capsaicin (8-Methyl-N-vanillyl-*trans*-6-nonenamide) is known to be an important stimulating factor [21]. Nociceptive sensory neurons also take part in protective reflexes, including the cough and sneeze reflexes, and release inflammatory neuropeptides in the periphery upon stimulation by different environmental stimuli. Patients with chronic cough had an increase of TRPV1-staining nerve profiles and, furthermore, a significant correlation between capsaicin tussive response and the number of TRPV1-positive nerves [22,23]. Several studies have shown that patients with chronic cough have increased capsaicin cough sensitivity [11,16]. The results from all these studies suggest that the pathophysiology of chronic persistent unexplained cough is related to airway mucosal TRP receptors on sensory nerves, as well reacting to noxious stimuli [19].

Also in asthma, rhinitis and COPD, airway symptoms induced by environmental irritants are common. These patients often complain of symptoms induced by exposure to cold air, smoke, exhaust fumes, strong odorants, and exercise. Although the role of sensory nerves in airway inflammation and obstruction is controversial, there is a growing body of evidence that sensory nerves mediate many of the symptoms in these patients [24]. In line with this, patients with asthma/COPD and allergic rhinitis exhibit, respectively, an exaggerated cough and secretory response to the sensory nerve stimulant capsaicin [11,16,25]. The link between the inflammatory cascade of asthma, causing bronchial hyperreactivity, and the axon reflex of bronchoconstriction is although intensive research still not clarified [26]. Increasing evidence points to a potential role for members of the TRP family of cation channels on airway sensory non-adrenergic non-cholinergic (e-NANC) nerves in the development of bronchial hyperreactivity and several features of asthmatic disease [19,26,27].

Capsaicin in food

Capsaicin is found naturally in a great variety of food dishes comprising different kinds of chili products and gives a "hot" taste. The use of chili in food varies between different countries and cultures. Most western countries have no long tradition of the use of chili in cooking. A dish with a lot of hot chili can result in undesired symptoms like irritation in the mouth and throat, sneezing, eye irritation and sometimes coughing. It is "common

knowledge" that it is possible to get used to spicy food by gradually increase the intake. The more you eat, the fewer symptoms you get. The scientific explanation to this phenomenon is on receptor level. The TRPV1 receptors, which are activated by capsaicin use neuropeptides to evoke brain signals and if you regularly stimulate these receptors with capsaicin rich food the neuropeptides are depleted and no or few symptoms are awaked by spicy food.

Pain and TRPV1

The TRPV1 receptor is also known to react to pain stimuli and mirror pain sensitivity [28]. For a long time, different pain conditions (arthritis, cystitis, human immunodeficiency virus, and diabetic neuropathy) have been treated with topically applied capsaicin (crèmes, gels and patches) [28,29]. A recently developed site-specific capsaicin therapy with high-dose patches and injectable preparations seem to be safe and reportedly provide long-lasting analgesia with rapid onset [30].

Gastrointestinal symptoms and TRPV1

In the gastrointestinal system the TRPV1 receptors are widely represented and some researchers make a connection between these receptors and chronic symptoms like irritable bowl syndrome (IBS) and have shown increased expression of TRPV1 receptors in this condition [31]. Recent studies show improvement of IBS and gut pain sensitivity after regular intake of capsaicin powder [32-37].

Cough and TRPV1

Capsaicin provokes cough when inhaled via the TRPV1 receptors and has for several years been used in the study of cough and is regarded to be to be an extremely safe research tool with no serious adverse reactions reported over the past 2 decades [38]. The capsaicin cough sensitivity increases during airway infections and is also heightened in different well-defined pulmonary conditions like asthma, COPD and pulmonary fibrosis [8,39-42]. In chronic cough without evident medical explanation and in SHR there is remarkably increased cough sensitivity to inhaled capsaicin [8,11,43].

In summary, testing with inhaled capsaicin is a well-documented tool in the diagnostics of chronic cough induced by environmental irritants where no evident other explanation to the cough, like asthma or allergy, has been found. The present invention is based on the idea that capsaicin could be used not only as an indicator but as a cure for cough which could be used for a down-regulation of coughing following a regular consumption of a

capsaicin product. Patients with chronic persistent unexplained cough will probably benefit most from the invention but also in rhinitis and other conditions known to have cough symptoms and increased cough reflex sensitivity the invention can improve symptoms.

A first object of the invention is to treat patients with different kinds of cough symptoms or increased cough reflex sensitivity, using a regular and oral administration of a capsaicin product. A more specific object of the invention is to treat patients with chronic persistent unexplained cough, using a regular and oral administration of a product containing capsaicin.

Another object of the invention is to provide a food additive, pharmaceutical preparation or the like for oral intake, for example formulated as a tablet, capsule, powder, syrup, drink or other suitable formulations that comprises capsaicin.

Accordingly, the present disclosure includes use of capsaicin and/or capsaicinoid in an oral dosage form for the treatment of cough hypersensitivity syndrome in a human subject, wherein cough hypersensitivity syndrome is a non-allergic chronic persistent unexplained cough lasting eight weeks or more.

Other objects and advantages of the present invention will become obvious to the reader and it is intended that these objects and advantages lie within the scope of the present invention.

Detailed description of the invention and preferred embodiments thereof

Capsaicin is found naturally in a great variety of food dishes comprising different kinds of chili products and gives a "hot". The invention herein concerns a new oral application for a capsaicin product to relive and reduce coughing related to other irritants then the capsaicin itself. Cough is an essential protective physiological mechanism to prevent food and liquid, dust, and chemicals to reach the lower airways, but it is also a symptom of many inflammatory diseases of the lungs. Patients with cough without any obvious explanation to the problem are often seen in clinical care and cough is arbitrarily defined as being chronic when it has lasted for more than 8 weeks. In the present application such patients will be referred to as having chronic persistent unexplained cough.

Capsaicin is known to induce cough. To the contrary of present knowledge we have found and made the invention herein that relates to a down-regulation of coughing following a regular consumption of a food additive, pharmaceutical preparation or the like for oral intake, for example formulated as a tablet, capsule, powder, syrup, drink or other suitable formulations that comprises capsaicin. Patients with chronic persistent unexplained cough will probably benefit most from the invention but also in rhinitis and other conditions known

to have cough symptoms and increased cough reflex sensitivity the invention has a potential to improve symptoms.

The capsaicin should be administered orally in low doses to induce desensitisation also against other irritants than capsaicin itself.

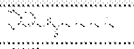
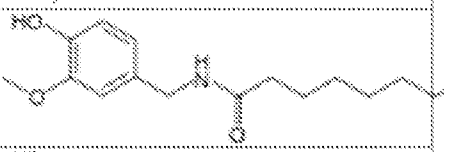
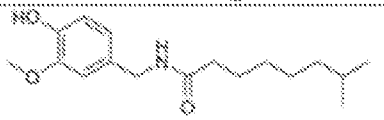
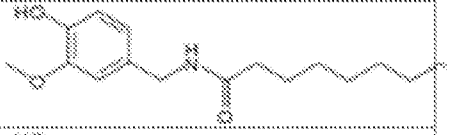
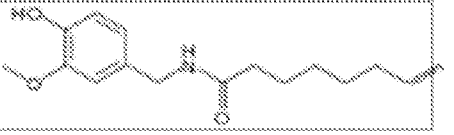
Chronic cough without evident medical explanations and also the cough component in sensory hyperreactivity (SHR) depend on an up regulation of the TRPV1 receptor system on airway sensory nerves. In parallel with the use of capsaicin in other conditions to improve for example pain and gastrointestinal symptoms, regular intake of a food additive comprising capsaicin (chili powder) will decrease the cough reflex sensitivity and improve cough symptoms by a continuous depletion of neuropeptides. Also other non-allergic airway and mucosal symptoms without evident cause may benefit from capsaicin, e.g. rhinitis, asthma-like symptoms, non-allergic eye irritation and burning moth syndrome. This may be the cause also in more general symptoms, from chemical and environmental sensitivity.

Following this the invention could be used also in the treatment of cough in common cold, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis and asthma (in these conditions the capsaicin cough sensitivity is known to be up regulated), non-allergic rhinitis, asthma-like symptoms, eye irritation, burning moth syndrome and different general symptoms caused from environmental sensitivity like headache, nausea and fatigue.

The administration of the product could be oral but also local by gargling, chewing of tablets or gums, or spraying, nasal or bronchial inhaling of aerosols or powder.

Capsaicin (8-methyl-n-vanillyl- 6-nonenamide, Chemical Abstracts Service (CAS) registry number is 404-86-4) as used herein may comprise pure capsaicin, and other capsaicinoids such as dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin etc. and may also be in diluted form, calculated to be used in equivalent strength, such as chili pepper powder or other powders or the like. By equivalent to capsaicin is thus meant a calculated strength firstly based on the form of capsaicinoid according to Table 1 and secondly if the active material is from a source which is not pure capsaicinoid such as chili-powder (which typically contains 0,4% pure capsaicin) and thirdly if also such material as chili-powder is diluted with a filler or the like. For example if undiluted chili-powder is used in a product of the invention which is targeted at a 0,4 mg capsaicin level, the amount of chili-powder to get to the equivalent strength is 100 mg.

Table 1: Examples of capsaicinoids

Capsaicinoid name	Abbrev.	Typical equivalent strengh	Scoville heat units	Chemical structure
Capsaicin	C	100%	16,000,000	
Dihydrocapsaicin	DHC	32%	16,000,000	
Nordihydrocapsaicin	NDHC	10%	9,100,000	
Homodihydrocapsaicin	HDHC	1,5%	8,600,000	
Homocapsaicin	HC	1,5%	8,600,000	

Preferably the daily doses of pure capsaicin, or equivalent, may vary from 0.01 mg to 100 mg, more preferably from 0.05 mg to 10 mg and most preferably from 0.2 mg 4 mg. The daily doses may be distributed one or several times a day, preferably between 1 to 5 times a day, commonly between 2 – 3 times a day. The daily doses is preferably distributed as unit dosages wherein each unit dosage may have a content of pure capsaicin, or equivalent, from 0.01 mg to 20 mg, more preferably from 0.05 to 5 mg and most preferably from 0.1 to 2 mg.

EXAMPLE 1

Natural chili pepper powder in capsules. The capsules are made from pectin that easily is digested in the stomach. Each active capsule comprises 100 mg chili powder of which 0.4% (0.4 mg) is a capsaicin compound. (Heinrich Klenk GmbH & CO KG, Germany) from chili powder, which is certified by European standard; European Pharmacopeia V; 2005 Cayennepepper, Capsici fructus, p.1662-1663. The powder is made from natural milled chili pepper and comprises 0.4% chili as capsaicin, dihydrocapsaicin and nordihydrocapsaicin.

The capsaicin in the capsules may also be pure capsaicin extracted from natural chilli fruits (Sigma-Aldrich, Sweden AB, Stockholm, M2028). Each active capsule will then comprise 0,4 mg pure capsaicin together with a filler material (cellulosa or sugar). Each capsule will then contain 100 mg (0,04 mg pure capsaicin together with 99,96 mg filling material.

EXAMPLE 2

The aim was to study whether a regular, standardized oral intake of natural capsaicin (chili powder) equal to a diet with very spicy food can improve cough symptoms and decrease cough reflex sensitivity measured by a standardized capsaicin inhalation cough test.

Study group

25 consecutively selected patients, having chronic refractory unexplained cough and claiming sensitivity to environmental irritants like perfumed products and chemicals participate together with 25 healthy control subjects. None of the participants have any other pulmonary or respiratory illness like allergy, asthma or chronic obstructive pulmonary disease (COPD).

Study design

Each participant visits the asthma and allergy clinic at Sahlgrenska University Hospital in Gothenburg, Sweden 3 times during a 8 weeks study period before the start of the study and after 4 and 8 weeks. At each visit cough sensitivity is assessed by a standardized capsaicin inhalation cough test [14]. During the 8 weeks the participants daily fill in a "patient symptom diary". During 4 weeks the participants take active capsaicin food additive capsules (chili powder) and during one month placebo capsules. The order of this is cross over, randomized and double blind.

Table 2: Flow scheme

Baseline visit all participants	2 weeks	2weeks	Half time visit all participants Cross-over	2 weeks	2 weeks	End visit all participants
Group A 12 pat + 13 cont	Capsaicin 0.4 mg, 1 x 2	Capsaicin 0.4 mg 2 x 2	Group A	Placebo 1 x 2	Placebo 2 x 2	Group A
Capsaicin test Questionnaires all participants	Symptom-diary	Symptom-diary	Capsaicin test Questionnaires all participants	Symptom-diary	Symptom-diary	Capsaicin test Questionnaires all participants
Group B 13 pat + 12 cont	Placebo	Placebo	Group B	Capsaicin 0.4 mg 1 x 2	Capsaicin 0.4 mg 2 x 2	Group B

The food additive

As per Example 1. During the active treatment period, the first two weeks, the participants take 1 capsule morning and evening and during the next two weeks 2 capsules morning and evening. All capsules are taken in connection to a meal.

Questionnaires

- Local questionnaire regarding general health and airway sensitivity to chemicals and scents
- The CSS-SHR (chemical sensitivity scale sensory hyperreactivity): estimating social and emotional influence from chemicals and scents
- The Hull cough questionnaire
- Symptom diaries for 8 weeks

Patients – inclusion criteria

- Age 18-70 years
- Airway sensitivity from chemicals and scents
- Daily cough symptoms
- Positive capsaicin inhalation cough test
- No gastrointestinal symptoms or problems
- Otherwise healthy
- Not pregnant or breast feeding
- No airway infection the last 4 weeks

Results

The capsaicin cough thresholds are significantly heightened. The daily symptom diaries show gradually significant improvement in all patients with 16 of them having no cough symptoms at all during the last week of active treatment. In patients starting with active treatment during 4 weeks the cough symptoms return after 2 placebo weeks and also the capsaicin cough thresholds are significantly lowered (impaired) after 4 placebo weeks compared to 4 weeks with active treatment.

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CLAIMS:

1. Use of capsaicin and/or capsaicinoid in an oral dosage form for the treatment of cough hypersensitivity syndrome in a human subject, wherein cough hypersensitivity syndrome is a non-allergic chronic persistent unexplained cough lasting eight weeks or more.

2. Use of capsaicin and/or capsaicinoid in the manufacture of an oral dosage form for the treatment of cough hypersensitivity syndrome in a human subject, wherein cough hypersensitivity syndrome is a non-allergic chronic persistent unexplained cough lasting eight weeks or more.

3. The use according to claim 1 or 2 wherein said unit dosage form contains 0.05 mg to 5 mg capsaicin and/or capsaicinoid.

4. The use according to claim 1 or 2 wherein said unit dosage form contains 0.1 to 2 mg capsaicin and/or capsaicinoid.

5. The use according to any one of claims 1 to 4, wherein the capsaicin and/or capsaicinoid comprises dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and/or homocapsaicin.

6. The use according to any one of claims 1 to 5 wherein the oral dosage form is in the form of a tablet, capsule, liquid, chewing gum, syrup or drink.

7. The use according to any one of claims 1 to 5 wherein the oral dosage form is in the form of a tablet or a capsule.

8. The use according any one of claims 1 to 7, wherein the capsaicin and/or capsaicinoid is for administration between 1 to 5 times a day.

9. The use according any one of claims 1-7, wherein the capsaicin and/or capsaicinoid is for administration 2 to 3 times a day.

10. The use according any one of claims 1-7, wherein a single dose of the capsaicin and/or capsaicinoid is for administration 2 to 3 times a day for an initial two week period and then two doses of the capsaicin and/or capsaicinoid are for administration 2 to 3 times a day for an additional two week period.

11. The use according any one of claims 1-10, wherein the capsaicin and/or capsaicinoid is the only active ingredient in the oral dosage form.