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Title

Therapeutic applications of capsaicin in humans to target conditions of the respiratory system: a scoping review

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NT designed and conducted the study. AE, AL, and STK contributed to the study conceptualisation and design, and supported database searching and screening of records. NT synthesised the findings. AE, NT and STK prepared the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Abstract (250 of 250 words)

Background: Various studies have explored potential therapeutic applications of capsaicin in human medicine, for example in pain, obesity, cancer, cardiovascular and respiratory disease. The aim of this scoping review was to identify and chart available evidence on therapeutic applications of capsaicin in humans using any mode of capsaicin delivery to treat conditions of the respiratory system.

Methods: Electronic bibliographic databases (Web of Science, PubMed, Medline, ScienceDirect, Embase, Scopus) were searched from inception to 2021 to identify experimental studies reporting clinical outcomes of therapeutic applications of capsaicin. Studies with or without control group published in peer-reviewed journals were included. Animal studies, studies of human cell lines, and physiological proof of concept studies were excluded. Reviewer pairs independently double-screened 2,799 search results for inclusion.

Results: Twenty-three original studies were included. Capsaicin has been investigated for the treatment of non-allergic rhinitis (n=15), nasal polyposis (n=3), allergic rhinitis (n=2), unexplained chronic cough (n=2), and prevention of aspiration pneumonia (n=1). Modes of delivery included intranasal application (nasal spray, soaked pads, solution), inhalation, ingestion, and aural ointment. Seventeen studies reported positive effects of capsaicin on clinical outcomes for rhinitis, nasal polyposis, chronic cough, and pneumonia. Sixteen studies reported on the safety of capsaicin, with no reports of significant adverse events and overall fair to good patient acceptability.

Conclusion: While the evidence identified in this review has limited implications for clinical practice, studies support the general safety of capsaicin as administered in these studies and highlight emerging strands of research and clinical hypotheses which warrant further examination.

Keywords

Capsicum; Cough; Humans; Respiratory; Review Safety

MAIN MANUSCRIPT

1. Introduction

Chili peppers are fruits from the *Solanaceae* family, *Capsicum* genus. They contain pungent molecules such as capsaicin, dihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin, collectively known as capsaicinoids. Capsaicin is a commonly used capsaicinoid because of its wide therapeutic applications which include pain management,[1] treatment of obesity,[2] cancer,[3] cardiovascular disease,[4] and respiratory conditions.[5,6]

Repeated doses of capsaicin cause an initial sensation of pain succeeded by analgesia.[7] Hence, capsaicin can be used to alleviate pain in conditions such as peripheral diabetic neuropathy,[8] post-herpetic neuralgia,[9] complex regional pain syndrome,[10] neuropathic pain,[11] and postsurgical neuropathic pain.[12] Capsaicin usage to relief pain is usually achieved through topical/ external applications. There are also studies that have demonstrated the use of capsaicin intranasally for the prevention of cluster headaches.[13] A study conducted by Irving et al.[14] reported that post-herpetic neuralgia patients displayed a significant decrease in pain for 12 weeks when an 8% capsaicin patch was used. Oral capsaicin treatment briefly seized pain caused by oral mucositis in cancer patients during chemotherapy or radiotherapy.[15] Moreover, Zis et al.[12] reported the use of an 8% capsaicin patch on a post-traumatic neuropathic pain patient, which resulted in the reduction of the allodynia area by 80% up to 18 months after the application.

Multiple studies have indicated that capsaicin elicits its anti-obesity effect through the activation of transient receptor potential vanilloid 1 (TRPV1).[16] TRPV1 influences energy metabolism and has a role in the prevention of obesity.[17] It also plays a role in glucose and lipid metabolism.[18] Once TRPV1 is activated by capsaicin, it stimulates the secretion of insulin and increases glucagon-like peptide-1 (GLP-1) levels, which causes a reduction in the abnormal glucose levels.[19] Besides it was reported that TRPV1 channels are downregulated in normal adipogenesis and calcium influx decrease synonymously. The use of capsaicin on 3T3-L1-preadipocytes suppresses adipogenesis and increases calcium influx in a dose-dependent manner.[20] In the study conducted by Ohnuki et al.[21] mice were treated with capsaicin (10 mg/kg body weight) and this enabled the increase of metabolic energy and reduced the body fat accretion.

The ingestion of capsaicin from a spicy diet was previously thought to be related to an increase in gastrointestinal cancer.[22] However, more contemporary research has indicated a role of pure capsaicin in the prevention and treatment of cancer through effects of capsaicin on the expression of numerous genes that are related to survival,[23] growth arrest,[24] angiogenesis,[25] and metastasis of cancer cells.[26] In numerous types of cancer, capsaicin's pro-apoptotic activity is believed to be mediated by the TRPV1 receptor.[27] TRPV1 is expressed in brain, bladder, kidney, and intestine tissue as well as mast cells and macrophages.[28] TRPV1 has been found to be expressed in most analysed tumour cells.[29] Moreover, capsaicin is believed to prompt phosphorylation of p53 at the Ser-15 residue that is responsible for apoptosis activation.[30] A study by Sarkar et al.[31] incubated human gastric adenocarcinoma cells (AGS) with different concentrations of capsaicin. Capsaicin was discovered to stimulate apoptosis in AGS cells by upregulating p53. Additionally, the study found that capsaicin's apoptotic activity is p53-dependent.[31] These findings were also confirmed by earlier reports by Park and co-workers[32] who studied the effect of capsaicin on AGS cells and found that exposure to capsaicin increases caspase-3 activity (pro-apoptotic protein). This confirms that capsaicin exhibits anti-tumorigenic activity in human gastric cancer.[32]

The management of cardiovascular conditions is another therapeutic area where capsaicin has shown beneficial effects. Capsaicin-sensitive sensory nerves regulate cardiovascular function by releasing neurotransmitters, in particular calcitonin gene-related peptide (CGRP) and substance P.[33] CGRP is a potent vasodilator that plays a major role in regulating blood pressure.[34] Capsaicin decreases blood pressure by activating TRPV1 receptors, thereby inducing CGRP release.[35] A study by Xu et al.[36] found that by increasing the phosphorylation of PKA and endothelial nitric oxide synthase through TRPV1 activation, dietary capsaicin in hypertensive stroke-prone rats led to a reduction of blood pressure in addition to delaying stroke onset. Furthermore, a study by Ma et al.[17] reported that by activating TRPV1, capsaicin decreases lipid storage as well as atherosclerotic lesions in the aortic sinus and in the thoracoabdominal aorta in mice. In addition, capsaicin causes deceleration to the atherosclerosis process through activating TRPV1 by stimulating autophagy in oxidized low-density lipoprotein in vascular smooth muscle cells that are treated with capsaicin.[37] LDL oxidation is also a rate limiting factor for atherosclerosis development. A study by Ahuja et al.[38] showed that capsaicin slows the rate of oxidation of LDL in vitro. Additionally, consumption of chilli regularly for 4 weeks in men and women has been found to increase lipoprotein resistance to oxidation.[4] This demonstrates capsaicin's important role in preventing cardiovascular disease.

With respect to the respiratory applications of capsaicin in humans, the use of capsaicin is most established for diagnostics and outcome assessments in the research setting. Capsaicin is used as a nebulised irritant for reflex cough sensitivity testing,[39,40] for example in the assessment of the effectiveness of cough suppressant medication,[41] or to assess the integrity of the cough reflex in neurological patients.[42] In addition to this established diagnostic use, several potential therapeutic benefits of capsaicin in respiratory conditions have been explored, for example as a treatment for rhinitis[43] and to prevent pneumonia;[6] and a hypothesised mechanism of action of inhaled nebulised capsaicin for the treatment of retained excess respiratory secretions has been described.[44]

The aim of this scoping review was to identify and synthesise the scientific literature on therapeutic applications of capsaicin in humans which target medical conditions of the respiratory system (upper or lower airways). The research question was "What are the therapeutic uses of capsaicin in the treatment of respiratory conditions in humans?" The objectives were to describe (a) target conditions, (b) modes of capsaicin delivery, (c) study designs and levels of evidence, (d) treatment effects, and (e) safety of capsaicin.

2. Method

We conducted a scoping review with descriptive summary of findings. A scoping review is the appropriate study design for identifying available research literature and mapping current evidence.[45] The study protocol was not registered or published. Study reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (extension for scoping reviews, PRISMA-ScR).[46] The PRISMA-ScR checklist is provided in online supplemental file 1.

2.1. Eligibility criteria

Eligibility criteria were defined using the Population – Intervention – Comparator – Outcomes (PICO) model (table 1). Additional eligibility criteria relating to study design, language, and publication status were as follows: Eligible articles were primary research studies including study designs with and without control group, i.e., randomised controlled trials, quasi- or non-randomised controlled studies, pre-post studies without control group, n-of-1 studies, case series, or individual case studies. Publications in all languages represented within the reviewer team were eligible (Arabic, English,

German, Polish). Only full research articles published in peer reviewed scientific journals were eligible. There were no restrictions regarding the date of publication.

Table 1. Eligibility criteria according to the Population – Intervention – Comparator – Outcomes (PICO) model.

Concept	**Inclusion criteria**	**Exclusion criteria**
Population	Humans, including healthy individuals and patients	Animal studies, studies of human cell lines
Intervention	Interventions which (1) deliver capsaicin (including nebulisation/inhalation, nasal spray, topical or oral administration, ingestion) *and* (2) aim to treat a condition of the respiratory system (upper or lower airways)	Interventions in which capsaicin is administered to the respiratory system, or administered to act on physiological mechanisms of the respiratory system, but which are not directly targeting medical conditions of the respiratory system
Comparator	Any comparator applied in a controlled study design, e.g., alternative drug, placebo, usual care, or no care; studies without comparator/control group are also included	None
Outcome	Outcomes relating to the effectiveness of the intervention in treating medical conditions of the respiratory system; outcomes relating to safety of capsaicin	Studies which do not report outcomes directly related to medical conditions of the respiratory system

2.2. Search strategy

Following initial scoping searches using Google Scholar, studies were identified by systematically searching electronic bibliographic databases such as Web of Science, PubMed, Medline, ScienceDirect, Embase and Scopus (from inception to present). The initial searches were performed on 29 June, 7 July, and 4 August 2020. The searches were updated on 12 and 27 March 2021.

The search strategy included the terms ‘capsaicin’ and ‘resiniferatoxin’, a functional analog of capsaicin, in combination with different respiratory search terms such as ‘respiratory applications’, ‘airways’, and ‘pulmonary’. A list of the databases and search terms used is given in table 2.

In addition to searching bibliographic databases, further potentially relevant articles were identified by hand-searching the reference lists of any relevant systematic reviews and of all included research articles; and through citation searches for all included research articles using Google Scholar.

Table 2. Summary of search strategy including databases, search fields, and search terms used.

Database (search fields)	Search terms
PubMed (all fields)	capsaicin AND respiratory; capsaicin AND cough AND inducer; capsaicin AND respiratory AND applications; capsaicin AND respiratory AND use; capsaicin AND resiniferatoxin; resiniferatoxin AND lung; resiniferatoxin AND respiratory
ScienceDirect (all fields)	capsaicin AND respiratory; capsaicin AND respiratory AND applications; capsaicin AND respiratory AND use
Medline (all fields)	capsaicin AND respiratory; capsaicin AND cough AND inducer; capsaicin AND cough; capsaicin AND airways; capsaicin AND bronchial; capsaicin AND lung; capsaicin AND nasal; capsaicin AND pulmonary; capsaicin AND trachea
Web of Science (all fields)	capsaicin AND respiratory AND uses; capsaicin AND respiratory AND applications
Scopus (title, abstract, keywords)	capsaicin AND respiratory; capsaicin AND respiratory AND use; capsaicin AND lung; capsaicin AND nasal AND polyps
Embase (all fields)	capsaicin AND (respiratory applications OR cough inducer OR respiratory OR lung OR airways OR pulmonary OR bronchial OR trachea OR nasal OR cough OR nasal polyposis)

2.3. Study selection

Two reviewers independently screened titles and abstracts of all search results against eligibility criteria. Where the title and abstract were relevant, the full text was then screened. Disagreements between the two reviewers were resolved by involving a third reviewer.

2.4. Data extraction and charting

Data were extracted using data extraction forms in Microsoft Word. The following information was extracted: first author, year of publication, journal, doi, country, title, study aim, target disease/condition, study design, participant characteristics, capsaicin intervention (proposed mechanism of action, formulation, mode of delivery, duration), comparator details (if any), outcome measures, results for each outcome measure, and safety data (method and duration of safety monitoring, safety outcomes). Extracted data for each study were then charted according to information pertaining to either the therapeutic properties of capsaicin, the safety profile of capsaicin, or both.

For each included study, the level of evidence was determined according to the study design, using the hierarchy of evidence described by the Oxford Centre for Evidence-Based Medicine.[47–49] Included studies were not critically appraised.

2.5. Data synthesis

A narrative synthesis was conducted, addressing each study objective in turn. Study characteristics and results were summarised in tabular form. Studies were grouped according to target disease/condition to describe the effectiveness of capsaicin interventions in the treatment of medical conditions of the respiratory system. Safety information was summarised according to mode of delivery of capsaicin.

3. Results

After deduplication of database search records, a total of 1,855 records were screened against eligibility criteria. Hand-searching of reference lists, citation searches and updates of database searches identified an additional 944 records for screening. In total, 72 articles were retrieved for full-text assessment. The two main categories of excluded records were studies not investigating a therapeutic application of capsaicin (n=27) and publications other than full research articles (n=10). Further reasons for exclusion are detailed in the PRISMA flowchart (figure 1).[50] Twenty-four eligible articles reporting on 23 original research studies remained for inclusion in this review.

Included articles were published from 1991[51–53] to 2020.[6,54] The majority of this literature stems from continental Europe (n=17), while three studies were conducted in the United States, and one each in Australia, China, and Japan. Study characteristics are presented in table 3 and summarised here according to the specific objectives of this review.

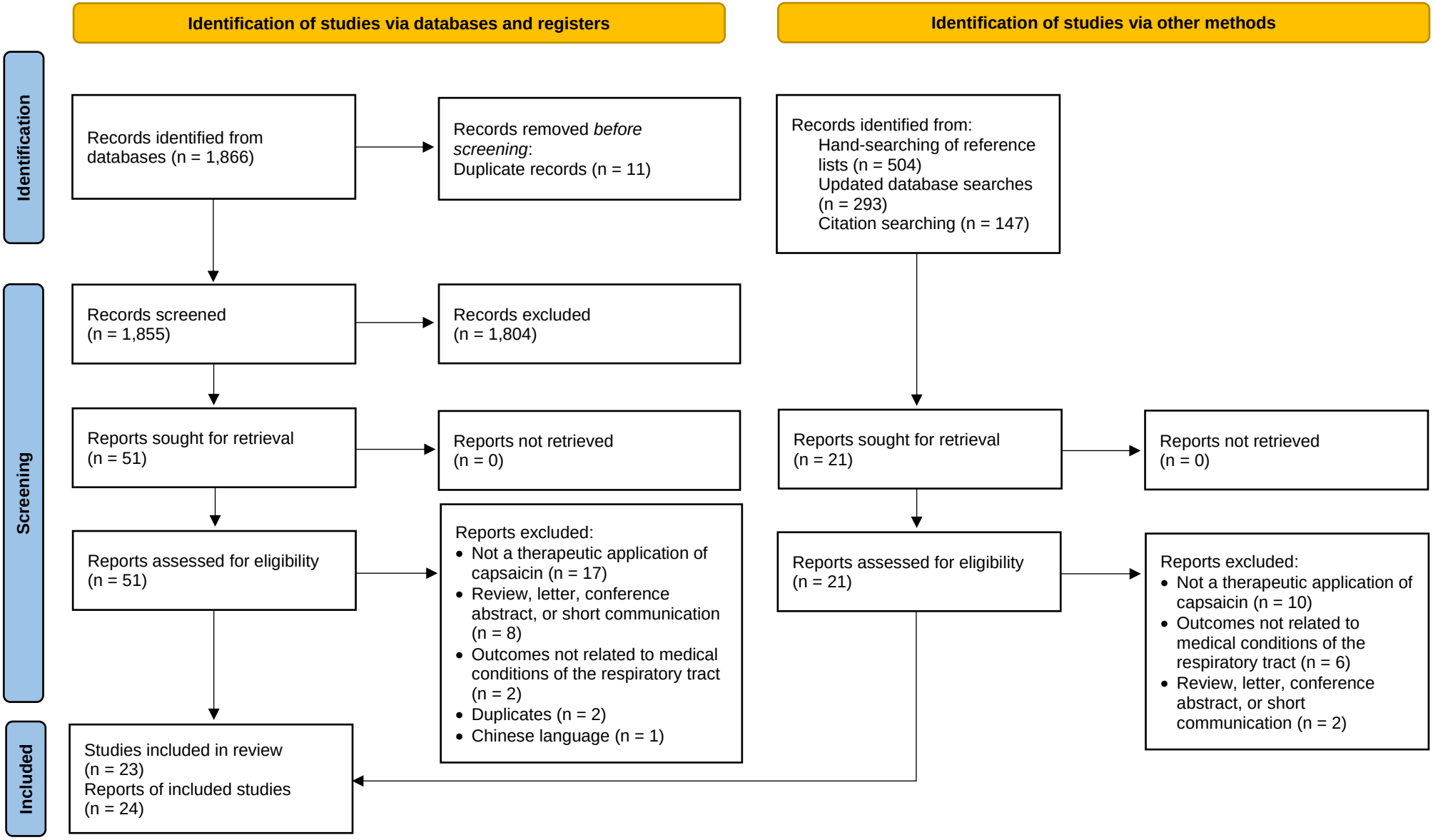
Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from databases (n = 1,866)
Records removed *before screening*: Duplicate records (n = 11)
Records identified from: Hand-searching of reference lists (n = 504) Updated database searches (n = 293) Citation searching (n = 147)
Records screened (n = 1,855)
Records excluded (n = 1,804)
Reports sought for retrieval (n = 51)
Reports not retrieved (n = 0)
Reports sought for retrieval (n = 21)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 51)
Reports excluded:
• Not a therapeutic application of capsaicin (n = 17)
• Review, letter, conference abstract, or short communication (n = 8)
• Outcomes not related to medical conditions of the respiratory tract (n = 2)
• Duplicates (n = 2)
• Chinese language (n = 1)
Reports assessed for eligibility (n = 21)
Reports excluded:
• Not a therapeutic application of capsaicin (n = 10)
• Outcomes not related to medical conditions of the respiratory tract (n = 6)
• Review, letter, conference abstract, or short communication (n = 2)
Studies included in review (n = 23)
Reports of included studies (n = 24)

Figure 1. PRISMA flow diagram.

Table 3. Characteristics of included studies (N=23). Studies have been grouped by target condition.

First author, year of publication	Target condition	Study design	Sample	Mode of delivery of capsaicin	Findings	Reported safety data	Level of evidence*
Bernstein, 2011[55]	Non-allergic rhinitis^	Randomised, placebo-controlled, double blind study	42 patients	Nasal spray	Treatment led to significant improvement in subjective nasal symptoms; no group difference in RQLQ quality of life score	Yes	Level 2
Blom, 1997, 1998[5,56]	Non-allergic, non-infectious perennial rhinitis (NANIPER) ^	Randomised, placebo-controlled, double blind study	25 patients	Intranasal puffs	Capsaicin led to significant and long-term reduction in subjective nasal symptom scores, no group difference in inflammatory mediators and nasal biopsy findings	Yes	Level 2
Ciabatti, 2009[57]	Idiopathic rhinitis	4-group randomised controlled trial (3 groups with different capsaicin doses, 1 placebo group)	208 patients	Capsicum oleous nasal spray	Significant reduction in nasal symptoms in the group receiving 4 µg/puff as compared to placebo, but not in the two other intervention groups	Yes	Level 2
Gerth Van Wijk, 2000[58]	Perennial allergic rhinitis to house dust mites^	Randomised, placebo-controlled, double blind study	26 patients	Nasal spray	No group differences in any outcome measures	No	Level 2
Ternesten-Hasseus, 2015[41]	Unexplained chronic cough triggered by environmental irritants	Crossover double-blind randomised controlled trial	24 individuals	Gelatin capsules	Chronic cough patients showed significant decrease in capsaicin cough sensitivity, improved cough symptoms, and improved cough scores	Yes	Level 2
Van Gerven, 2017[59]	Idiopathic rhinitis^	Randomised, placebo-controlled, double blind study	33 patients	Intranasal application of capsaicin	Treatment group showed significant reduction in nasal symptoms and self-rated improvement; and significant increase in threshold for nasal mucosal potential recordings	No	Level 2
Van Rijswijk, 2003[60]	Idiopathic rhinitis^	Randomised, placebo-controlled, double blind study	30 patients	Intranasal application (metered nasal spray)	Intervention group showed a trend towards greater improvement in outcomes	Yes	Level 2
Zebda, 2020[54]	Non-allergic rhinitis^	Randomised, placebo-controlled, double blind study	22 patients	Intranasal application (mucosal atomiser)	The treatment group showed a trend towards greater improvement in outcomes	No	Level 2

Zheng, 2000[61]	Nasal polyposis	Randomised, placebo-controlled, double blind study	51 patients	Intranasal cotton pellet soaked with capsaicin applied to both nostrils.	Treatment group showed significant improvements in self-reported NAR and clinical staging of polyposis; no group difference in rhinorrhoea	No	Level 2
Filliaci, 1996[62]	Aspecific nasal hyperreactivity with polyposis	Placebo-controlled, double blind study (method of group allocation not reported)	30 patients	Topical application of capsaicin in each nasal fossa.	Treatment group showed significant improvement in symptom scores for obstruction after 5 weeks and 3 months, improvement in nasal hyperactivity after 5 weeks, and increase in eosinophil level after 5 weeks	No	Level 3
Havas, 2002[63]	Non-infectious perennial rhinitis (NANIPER)^	Controlled study design with pseudo-randomisation	40 patients	Intranasal capsaicin spray	Significant improvement in nasal symptoms in the capsaicin group	Yes	Level 3
Stjärne, 1998[64]	Allergic rhinitis	Controlled study design (method of group allocation not reported)	9 patients	Cotton wads soaked in capsaicin solution in both nasal cavities/	Treatment group showed significant improvement in subjective symptoms upon allergen challenge; no group differences in nasal mucosal swelling or eosinophil migration to the nasal mucosa	Yes	Level 3
Baudoin, 2000[65]	Sinonasal polyps	Clinical case series with pre-post outcome assessment	9 patients	Intranasal spray	4 weeks after treatment there were significant improvements in major symptom scores, endoscopy scores, and mean NSAV; ECP levels showed a trend towards increase after capsaicin	No	Level 4
Eberle, 1994[66]	Vasomotor rhinitis / hyperactive rhinopathy^	Clinical case series with pre-post outcome assessment	84 patients	Nasal spray	Post treatment, self-reported symptoms and observer-rated turbinate hypertrophy resolved in half to two thirds of patients, and average nasal flow improved	Yes	Level 4
Filliaci, 1994[67]	Vasomotor rhinitis of non-allergic origin^	Clinical case series with pre-post outcome assessment	10 patients	Topical application of a soaked buffer	Improvements in nasal symptoms and nasal obstruction, normalisation of aspecific hyperreactivity	Yes	Level 4
Jinnouchi, 2020[6]	Pneumonia	Clinical case series with retrospective control period	29 inpatients	Capsaicin ointment applied to the external auditory canal.	Significantly lower incidence of pneumonia during the 6-months treatment period compared to the preceding 6-months	Yes	Level 4

Lacroix, 1991[51]	Non-allergic chronic rhinitis^	Clinical case series with pre-post outcome assessment and healthy control group	16 patients,	Intranasal spray	Reduction of nasal vascular responses, subjective nasal symptoms, and CGRP-LI content following capsaicin treatment	Yes	Level 4
Marabini, 1991[52]	Vasomotor rhinitis^	Clinical case series with pre-post outcome assessment	20 patients	Nasal spray	Approx. 50% reduction in subjective symptoms in all patients	Yes	Level 4
Riechelmann, 1993[68]	Non-allergic rhinitis^	Clinical case series with pre-post outcome assessment	27 patients	Intranasal nebulised capsaicin	Mixed findings for nasal symptoms and rating of treatment success, no statistically significant results	Yes	Level 4
Slovarp, 2019[69]	Unexplained chronic cough	Case series with pre-post outcome assessment	5 healthy volunteers	Inhalations	Post treatment, reflex cough sensitivity improved (higher concentrations of capsaicin required to elicit cough)	Yes	Level 4
Stjärne, 1991[53]	Non-allergic nasal hyperreactivity^	Clinical case series with pre-post outcome assessment	10 patients	Cotton wads soaked in capsaicin solution	Patient's nasal symptoms significantly improved post-treatment and reverted to pre-treatment levels at the 6-month follow-up; individual reaction to capsaicin challenge corresponded with individual subjective symptom scores	Yes	Level 4
Van Gerven, 2014[70]	Idiopathic rhinitis^	Clinical case series with pre-post outcome assessment	14 patients	Intranasal application of capsaicin	Patients showed significant reduction in nasal symptoms and positive trend in self-rated improvement	No	Level 4
Wolf, 1995[71]	Vasomotor rhinitis^	Clinical case series with pre-post outcome assessment	123 patients	Topical application to both nasal cavities	Self-reported symptoms improved in half to two thirds of patients; average nasal flow and sensitivity to capsaicin improved	Yes	Level 4

* Levels of evidence according to Oxford Centre for Evidence-Based Medicine hierarchy of evidence[47-49]

^ Non-allergic rhinitis includes vasomotor rhinitis, idiopathic rhinitis, non-allergic chronic rhinitis, non-allergic nasal hyperreactivity, and non-allergic non-infectious perennial rhinitis (NANIPER)

3.1. Target conditions

The majority of studies investigated capsaicin for the treatment of non-allergic rhinitis (n=15).[5,55–57,59,60,63,66–68,70,71] This grouping includes all studies using the descriptors non-allergic (chronic) rhinitis, vasomotor rhinitis, idiopathic rhinitis, non-allergic nasal hyperreactivity, and non-allergic non-infectious perennial rhinitis (NANIPER). Other target conditions were nasal polyposis (n=3),[61,62,65] allergic rhinitis (n=2),[58,64] unexplained chronic cough (n=2),[41,69] and pneumonia (n=1).[6]

3.2. Modes of capsaicin delivery

In those studies that targeted intranasal conditions (*i.e.*, rhinitis or nasal polyposis), capsaicin was administered to the nasal cavity primarily by intranasal spray (n=15),[5,51,52,54–60,63,65,66,68,70,71] by packing pads soaked with capsaicin solution into the nasal cavity (n=4),[53,61,64,67] or by direct application of capsaicin solution into the nasal fossa (n=1).[62] In the two studies that targeted unexplained chronic cough, capsaicin was delivered by inhalation[69] and by ingestion.[41] In the study that targeted pneumonia, capsaicin ointment was applied to the external auditory canal.[6]

Capsaicin dosage in aerosolised application (nasal spray, inhalation) ranged from 0.1-4 µg/puff and each puff of volume of 70 µL, and in one instance a homoeopathic preparation of capsaicin was delivered.[55] Capsaicin solutions applied to the nasal cavity directly ranged in concentration from 10-100 µM. In two thirds of these studies (15 of 21), a local anaesthetic such as lidocaine, cocaine or tetracaine was used to numb the nasal mucosa prior to the application of capsaicin. While some studies used local anaesthesia to improve blinding in placebo-controlled study designs – reducing the possibility that patients could deduce from the burning or painful sensation (or lack thereof) that they had received capsaicin (or placebo) – the main reason for anaesthesia in most studies was to reduce capsaicin-induced discomfort and improve patient acceptance of the treatment. In these studies, the frequency and duration of capsaicin treatment ranged from single-day treatments (5 consecutive applications in 1-hour intervals)[54,59,60,70] to daily applications over five weeks.[59,60,67]

In the only study that administered capsaicin per os, the dosage for ingestion was 0.4 mg capsaicin once or twice per day over 4 weeks.[41] In the study that applied capsaicin to the external auditory canal, the ointment contained 0.025% capsaicin and was administered daily over 6 months.[6]

3.3. Study designs and levels of evidence

Eleven studies were clinical case series or uncontrolled cohort studies with pre-post outcome assessment,[6,51–53,65–71] with sample sizes ranging from N=5[69] to N=123.[71] These studies were classified as level of evidence 4 according to the Oxford Centre for Evidence-Based Medicine hierarchy of evidence.[47–49]

Twelve studies had controlled study designs, with sample sizes ranging from N=9[64] to N=208.[57] Nine of these studies were randomised placebo-controlled trials.[5,41,54–61] The reported used placebos were NaCl, water, or the same solution/dilutant as for verum without the addition of capsaicin. All studies were double blinded, except for the study by Ciabatti et al.[57] All randomised controlled studies were classified as level of evidence 2. The study by Havas et al.[63] used pseudo-randomisation for group allocation, and the group allocation method was not reported for the studies by Filiaci et al.[62] and Stjärne et al.[64] For these three studies, the level of evidence was therefore downgraded to 3.

3.4. Treatment effects

Among studies of non-allergic rhinitis, 10 studies reported a positive treatment effect, and five reported mixed or inconclusive findings.[54,60,66,68,71] For allergic rhinitis, one study found a positive

treatment effect[64] and one found no difference between capsaicin and control group.[58] All three studies of nasal polyposis reported positive treatment effects. These 20 studies of non-allergic rhinitis, allergic rhinitis, and nasal polyposis primarily collected self-reported symptom outcome data, using Visual Analogue Scales or severity ratings for nasal congestion, rhinorrhoea, sneezing, *etc*. Additional objective outcome assessments in these studies included rhinomanometry, nasal provocation tests, endoscopy, and nasal biopsy or lavage, which largely corroborated the findings from subjective outcomes.

Both studies of unexplained chronic cough[41,69] reported positive treatment effects on reflex cough sensitivity as assessed by capsaicin inhalation challenge. The study by Ternesten-Hasseus et al.[41] additionally reported improvements in self-reported cough symptoms for the capsaicin treatment group. The primary outcome in the study by Jinnouchi et al.[6] was incidence of pneumonia during six months of capsaicin treatment as compared to the six months prior to commencing capsaicin treatment. The study found a reduction from an average of 1.8 to 0.4 chest infections per participant over the observation period.

3.5. Safety of capsaicin

Capsaicin safety data are presented in table 4. In summary, 16 out of 23 studies reported on the safety of capsaicin,[5,6,41,51–53,55–57,60,63,64,66–69,71] *i.e.*, authors of these study reports made explicit reference to safety, adverse effects, and/or side effects of the capsaicin intervention. The duration of safety monitoring ranged from three days[64] to six months[6,51,53,67,68] and mostly included participant self-report (*e.g*., using a daily self-report diary of symptoms and subjective rating of discomfort and pain) and history-taking by investigators during study appointments. Additionally, several studies included repeated clinical assessments such as smell tests, blood and urine sample analysis, blood pressure and pulse/heart rate measurements, and rhinoscopy. Overall, observed adverse effects were judged as minor by investigators and included transient discomfort (stinging, burning, pain) at the application site, itching, sneezing, coughing, and rhinorrhoea. In all studies, in which capsaicin was administered to the nasal cavity and in which participants' sense of smell was monitored, there was no adverse effect of capsaicin on participants' sense of smell.[51,55,60,63] Of note, both studies by Stjärne et al.[53,64] reported that intranasal application of capsaicin did elicit pain despite local anaesthesia, to an extent that could impact patient acceptability and clinical utility of the treatment. This might be related to the prolonged local application (15 minutes via soaked cotton wad) of capsaicin to the nasal mucosa in these two studies.

4. Discussion

This scoping review has identified a moderate-size body of literature and evidence on therapeutic applications and clinical outcomes of capsaicin in humans for medical conditions of the respiratory system (upper or lower airways). Most studies investigated intranasal administration of capsaicin (nasal spray or placement of capsaicin-soaked pads in the nasal cavity) for non-allergic rhinitis, allergic rhinitis, or nasal polyposis, while only three studies investigated capsaicin for conditions of the lower respiratory system (chronic unexplained cough and pneumonia) using capsaicin ingestion, inhalation, or ointment for aural stimulation. Other published reviews corroborate this picture, highlighting research activity around capsaicin in rhinitis and nasal polyposis.[43,72–75] The present review adds to the literature by also charting the more recent emerging body of research on capsaicin for the treatment of chronic unexplained cough[41,69] and for the prevention of pneumonia;[6] and by summarising the available safety data, demonstrating that capsaicin in these particular applications and dosages may generally be considered safe, with no reports of serious adverse events associated with the administration of capsaicin, and that these treatments offer overall fair to good patient acceptability.

The use of capsaicin as described in this review may appear contradictory at times, for example aiming to increase reflex cough sensitivity in the study by Jinnouchi et al.,[6] while aiming to dampen reflex cough in the studies by Ternesten-Hasseus et al.[41] and Slovarp et al.[69] This is explained by different mechanisms of action of capsaicin which are targeted according to the particular respiratory condition under investigation and which this review has mapped out.

The commonly proposed mechanism of action for capsaicin in treatment of rhinitis (non-allergic and allergic) is thought to be mediated by activation of TRPV1 ion channels, which desensitises the nasal sensory neural fibers and reduces nasal hyperresponsiveness.[5,56] This desensitisation and degeneration could mean that fewer neuropeptides (substance P, CGRP, etc.) are released locally in response to irritating stimuli such as cold dry air (antidromic effect). Also, irritating stimuli might cause lesser sensory neural central stimulation, thus avoiding central protective neural reflex mechanisms of secretion, extravasation and vasodilatation (ortho-dromic effect). The same mechanism of action has also been described for the treatment of nasal polyposis, by capsaicin reducing neurogenic phlogosis.[62]

In the context of chronic unexplained cough, capsaicin has been used widely in research since the 1980s for the purpose of assessment (as opposed to therapy), in determining reflex cough sensitivity through capsaicin inhalation cough challenge.[39,76] This standardised test involves the delivery of nebulised capsaicin solution for inhalation in serial doubling concentrations from 0.49 to 1,000 µM, either for a single breath or for a fixed time period of 15-60 seconds at each concentration. The concentrations of capsaicin causing two or five coughs (C2 and C5, respectively) are recorded, indicating the individual's threshold for eliciting a reflex cough response.[39] In the study by Slovarp et al.,[69] this same mode of capsaicin administration was applied with therapeutic intention, to desensitise the cough reflex through repeated exposure to capsaicin and ultimately reduce unexplained chronic coughing. In a small sample of five healthy volunteers, Slovarp et al. were able to demonstrate proof of concept and safety of this application of capsaicin. Importantly, the protocol employed by Slovarp et al. appeared to adequately account for tachyphylaxis (short-term desensitisation), which is known to occur during repeated inhalations of capsaicin in close temporal

proximity. To avoid any influence of tachyphylaxis and to ensure reproducibility of repeated cough challenge measurements, a minimum period of 1-2 hours between measurements is recommended.[39] While the exact cause of chronic unexplained cough is unknown, it is believed that a neuroplastic process is initiated as a response to airway inflammation. Cough hypersensitivity does not resolve spontaneously and is prolonged by continuous coughing.[77] Evidence suggests that a similar mechanism is responsible for chronic neuropathic pain and chronic rhinitis, both of which involve TRPV1 receptors.[78] It is argued that peripheral and central mechanisms mediate chronic refractory cough.[79] Ternesten-Hasseus et al. noticed that cough sensitivity is decreased after oral supplementation with capsaicin, and attributed this to the peripheral desensitisation of airway receptors by the drug, yet a central reflex desensitisation could also be involved as TRPV1 receptors exist in the central nervous system as well.[80]

The safety of capsaicin inhalation cough challenge has been documented in a review by Dicpinigaitis and Alva from 2005,[81] which reported on 4,833 research participants in 122 published studies with no serious adverse events. More recently in 2016, a detailed prospective investigation in 20 younger and 20 older adults by Brooks et al.[82] has provided further evidence of the safety of capsaicin inhalation cough challenge, with no reported short-term changes in systemic responses (blood pressure, pulse rate, oxygen saturation) and serial lung function testing, and no reported delayed adverse effects up to five days following exposure. Additionally, Brooks et al. provide recommendations for safety monitoring of capsaicin cough inhalation challenge.[82] The literature therefore offers strong evidence of the safety of capsaicin administration using the standard inhalation cough challenge protocol[39] and provides reassurance and guidance to investigators who look to explore this mode of capsaicin delivery for novel therapeutic approaches, such as the treatment of chronic unexplained cough;[69] or the facilitation of respiratory secretion clearance in patients with impaired volitional cough by means of capsaicin-induced reflex cough.[44]

The therapeutic use of capsaicin for the prevention of pneumonia is based on the rationale that certain patient groups, such as older patients with dementia and high care needs in the study by Jinnouchi et al.,[6] present with reduced reflex cough sensitivity; and that this, coupled with some degree of dysphagia, leads to diminished protection of the lower airways from aspiration and subsequent aspiration pneumonia. The authors hypothesised that capsaicin ointment applied to the external auditory canal could stimulate the auricular branch of the vagus nerve (Arnold's nerve) via TRPV-1 receptors and improve glottal closure and reflex cough via Arnold's ear-cough reflex.[6] This hypothesis is supported by three other studies published by the same group of investigators.[83–85] These three studies were not included in this scoping review, because study data did not include clinical outcomes which relate directly to the target medical condition, *i.e.*, pneumonia; but these studies instead examined the physiological effect of aural stimulation with 0.025% capsaicin ointment on patients' reflex cough[85] and swallowing function.[83–85] In 2014, Kondo et al.[83] reported improved swallowing function in instrumental evaluation of swallowing after a single application (n=16) and after a 7-day course (n=10) of treatment in patients with neurogenic and dementia-related dysphagia. This positive effect on swallowing was later replicated in a randomised placebo-controlled double-blind study of 20 patients with neurogenic dysphagia.[84] The most recent study from this group has demonstrated improved swallowing and heightened reflex cough sensitivity assessed by inhalation cough challenge in 11 institutionalised older adults with non-obstructive dysphagia.[85] With respect to adverse events, the authors reported that capsaicin ointment evoked a warm sensation in the external auditory canal in most patients,[83] but that there were no instances of significant adverse effects such as otalgia, headache, otitis externa, or myringitis.[83–85]

Another hypothesis of how capsaicin could reduce the risk of aspiration pneumonia has been described in the literature as early as 1993 by Ebihara et al.,[86] who proposed that the addition of low dose capsaicin to ingested liquid or food may stimulate swallowing and cough reflexes, thereby preventing aspiration pneumonia.[86,87] An underlying assumption to this rationale is that capsaicin acts in the oro- and laryngopharynx, and this is further supported by two studies which were not included in this scoping review, because study outcomes related to swallowing and cough function rather than directly to clinical outcomes of pneumonia.[88,89] Ebihara et al. in 2005[88] published a randomised placebo-controlled trial of four weeks daily treatment with trochisci containing 1.5 µg capsaicin in 64 nursing home residents. They observed significant improvement in swallowing function (latency of the swallowing reflex) and a trend towards greater improvement in reflex cough sensitivity in the intervention group.[88] More recently, the single-blind placebo-controlled study by Cui et al. published in 2020[89] examined the effect of stimulation with an ice swab from frozen 150 µmol/L capsaicin solution to the soft palate, posterior tongue, and pharynx in 92 dysphagic stroke patients. The study showed that after 3 weeks, there was greater improvement of swallowing function in the intervention group (standard swallowing assessment, water swallowing test).[89] Both studies reported no significant adverse effects of these applications of capsaicin.[88,89]

The body of evidence identified in this review is divided into methodologically stronger studies with controlled study designs, providing evidence levels 2 or 3; and weaker uncontrolled case series or cohort studies at evidence level 4. It is noteworthy that 17 of 23 studies reported positive findings for capsaicin, and only six studies in rhinitis reported findings of inconclusive effect or lack of effect of capsaicin. Particularly in novel and emerging areas of research, there can be a tendency to favour the early publication of promising findings over 'negative' results, which can lead to publication bias.[90] It may therefore be opportune to remind that publication of negative study findings is valuable, contributing to the balanced scientific appraisal of experimental treatments and reducing waste of resources in pharmaceutical and clinical research.[91]

With respect to recommendations for integration into routine clinical practice of the capsaicin treatments identified in this review, some current clinical practice guidelines for rhinitis include intranasal capsaicin as a treatment option for non-inflammatory non-allergic rhinitis, *e.g.*, Scadding et al.,[92] while other guidelines consider the evidence base insufficient to support such a recommendation, *e.g.*, Dykewicz et al.[93] The use of capsaicin in the treatment of allergic rhinitis is not recommended due to the very limited research evidence.[73,92,93] In nasal polyposis, current practice guidelines suggest that capsaicin may be considered an option in the treatment of chronic rhinosinusitis with nasal polyps, but caution that the evidence base is small and of low quality.[94] Regarding the treatment of unexplained chronic cough, desensitisation with agonists such as capsaicin is considered novel and experimental with need for more research.[76] The potential role of capsaicin in the prevention of (aspiration) pneumonia has been described repeatedly in the literature,[87,95–98] but remains experimental and is therefore not reflected in clinical practice guidelines.

4.1. Strengths and limitations of this review

Strengths of this review relate to the rigorous methodology, including comprehensive lateral literature searches, independent double-screening of database records, and study reporting according to the PRISMA-ScR statement.[46] This review is limited in that the included studies were ranked in the level of evidence according to study design, but not systematically assessed for their methodological quality. The findings from this review are therefore more appropriate for describing the literature and strands of research into therapeutic respiratory applications of capsaicin, as opposed to deriving concrete recommendations for clinical practice; and this is congruent with the

purpose of a scoping review which aims to provide a preliminary map of the evidence without appraising the quality and validity of results

5. Conclusion

This scoping review has identified and charted the available research evidence for therapeutic applications, clinical outcomes, and safety of capsaicin treatments in medical conditions of the respiratory system, including rhinitis, nasal polyposis, unexplained chronic cough, and pneumonia. While this body of literature has currently very limited implications for clinical practice, this evidence supports the general safety of capsaicin as administered in these studies and highlights emerging strands of research and clinical hypotheses which warrant further examination.

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