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The Effects of *Nigella Sativa* (Black Seed) in Rhinosinusitis Subjects: A Systematic Review

Muhamad Najmi Muhamad Najemudin[1], Muhamad Zafran Anas Mahmood[1], Syahrir Zaini[2] and Nurul Asyiqin Yusof[3*]

[1]*Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.*
[2]*Department of Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.*
[3]*Department of Basic Medical Sciences, Kulliyyah of Pharmacy, International Islamic University Malaysia, Jalan Sultan Ahmad Shah, 25200 Kuantan, Pahang, Malaysia.*

Abstract

Introduction: Allergic rhinitis is a persistent inflammatory nasal condition triggered by an exaggerated immune response to allergens. Its primary complication is sinusitis which progresses to rhinosinusitis. *Nigella Sativa* known for its anti-inflammatory effects, has shown promising efficacy in treating rhinosinusitis. While various studies have reported *Nigella Sativa's* effects on rhinosinusitis, there is paucity in specifically addressing the optimal therapeutic dose and efficacy compared to conventional anti-histamine or anti-allergic drugs. Thus, this study aims to systematically review the effects of *Nigella Sativa* on rhinosinusitis in both human and animal subjects. **Method**: This systematic review followed the guidelines of PRISMA. A systematic literature search was performed through searches in PubMed, Scopus, Cochrane Library, and Google Scholar, along with the application of the snowball technique. Two authors independently evaluated the identified articles at various stages, including title, abstract, and full text, against predefined eligibility criteria. The assessment of potential bias in the studies incorporated the Joanna Briggs Institute (JBI) checklist for critical appraisal of human studies and the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) tool for assessing bias in animal studies. **Results**: Twelve studies were included in this study. Six studies were found to exhibit a low risk of bias, whereas three studies were categorized with a moderate risk of bias, and an additional three studies were identified as having a high risk of bias. Seven studies recorded significant symptom reduction while other studies showed better histological changes and chemical parameters compared with conventional medication. **Conclusion**: *Nigella Sativa* demonstrates anti-inflammatory, anti-histaminic, and antimicrobial properties, aiding in alleviating symptoms of allergic rhinitis and rhinosinusitis. 10 to 100 mg/kg/day *Nigella Sativa* is proposed to be considered as the optimum dose range as an alternative to conventional drugs such as montelukast, mometasone furoate, and dexamethasone due to its minimal side effects.

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*Corresponding author's email: drnurul@iium.edu.my

Introduction

Allergic rhinitis (AR) is a prevalent, persistent inflammatory condition affecting the nasal passages, triggered by an exaggerated immune system response to allergens. According to the International Consensus Statement on Allergy and Rhinology (ICAR) 2023, it is primarily associated with a type 1 hypersensitivity reaction mediated by immunoglobulin E (IgE) (Sarah et al., 2023). It happens when allergens, like dust mites or pollen, bind to the nasal mucosa, triggering an IgE response that swiftly releases histamine. This process leads to allergic rhinitis symptoms such as sneezing, nasal congestion, and rhinorrhoea (Mims, 2014). There are two classifications of AR: (1) seasonal AR, linked to outdoor allergens and (2) perennial AR, associated with year-round indoor allergens. Additionally, allergic rhinitis has two sub-categories: (i) Intermittent AR, marked by symptoms less than four days per week or lasting less than four consecutive weeks and (ii) Persistent AR, characterized by symptoms occurring more than four days per week for at least one month (ICAR, 2023). The most common complication in AR is sinusitis, which is defined as inflammation of the paranasal sinuses caused by infection (Li et al., 2021). There are four classifications of sinusitis: (1) acute sinusitis, associated with the duration of symptoms between 10 days until less than 4 weeks, (2) sub-acute sinusitis, linked with duration of symptoms between 4 and 12 weeks (3) chronic sinusitis, similar to asthma with duration more than 12 weeks (Mahboubi, 2018) and (4) recurrent sinusitis, related to four or more episodes of sinusitis (Sharma et al., 2023). These two conditions often overlap which leads to rhinosinusitis (Helman et al., 2020). The existence of two or more primary symptoms such as blockage, drainage (anterior or posterior) and facial pain or pressure lasting for a minimum of 12 weeks, are validated through sinus endoscopy or computed tomography (CT) scan (Vlaminck et al., 2021).

AR affects 5 to 52% of the global population in 2020 (Oliveira et al., 2020). These figures may be greater in places with high allergen levels such as thick vegetation and increased exposure to environmental triggers. The prevalence of AR in the United States in 2020 was approximately 10% to 30% of adults and up to 40% of children (Dykewicz et al., 2020). It has become more common in several industrialised nations during the last few decades. The main causes of this rise are unknown, however, they might be ascribed to variables such as changes in environmental exposure, lifestyle, and urbanisation. In Singapore, the general prevalence of allergic rhinitis is estimated to range from 5.5% to 13%. Given the equatorial climate characterized by year-round warmth and humidity, persistent allergic rhinitis is the prevailing disease pattern (Liu et al., 2020). On the other hand, AR prevalence varied from 8.14 to 9.23% in the pre-pandemic period and from 1.83 to 6.40% in the post-pandemic phase in Malaysia (Chew et al., 2023). Malaysia's tropical setting and diverse plantations create a variety of allergens like pollen and mould spores, triggering allergic rhinitis symptoms in susceptible individuals. The increasing prevalence of this condition may also be influenced by lifestyle shifts and urbanisation (Chew et al., 2023). In Europe, passive smokers face a higher risk of allergic rhinitis compared to primary smokers, potentially worsening symptoms by heightening sensitivity to airborne allergens (Wu et al., 2021). On the other hand, rhinosinusitis affects 5% to 12% of the global population (Mullol et al., 2022) and 5% to 22% in the United States (Helman et al., 2020). In CPG Management of Rhinosinusitis in Adolescents and Adults (2016), it affects 8% in China and 2.7% in Singapore.

Nigella Sativa (NS) known as black seed or black cumin, belongs to the Ranunculaceae family and is native to regions in the eastern Mediterranean, northern Africa, the Indian subcontinent, and Southwest Asia (Hannan et al., 2021). It is a herbaceous annual plant that produces seeds that

are called black cumin or black seed, although, in old Latin, it was known as "*Panacea*" which means "cure-all", meanwhile in Arabic generally known as "*Habbat-uL-Sauda*", or "*Habbat el Baraka*" which means 'Seeds of blessings' (Nyemb et al., 2022). The botanical characteristics of NS consist of flowers that exhibit grace, primarily in shades of white, yellow, pink, light blue, or lavender colour boasting 5-10 petals each. Moreover, the fruits manifest as sizable, inflated capsules housing abundant black coats and white-content seeds possessing both aromatic and bitter flavours (Nyemb et al., 2022). The long-standing historical use of *Nigella Sativa* oil (NSO) and seeds in Indian and Arabic cultures spans various culinary and therapeutic applications. Traditionally, it has been employed to address conditions like asthma and hypertension, leveraging its potential health benefits including anti-inflammatory and immune-modulating properties, which could be beneficial in managing symptoms of allergic rhinitis (Mahboubi, 2018). The main bioactive compound in this plant is Thymoquinone (TQ) which exhibits anti-inflammatory effects and was found to be effective in suppressing histamine release from mast cells (Ikhsan et al., 2018). Meanwhile, it also demonstrated robust antimicrobial effects against both Gram-negative and Gram-positive bacteria, displaying minimum inhibitory concentration (MIC) values ranging from 8 to 512 μg/ml (Mahboubi, 2018). This evidence suggests that the anti-inflammatory and antimicrobial properties may help alleviate nasal inflammation and symptoms associated with allergic rhinitis and rhinosinusitis.

Currently, many strategies are being practised for managing allergic rhinitis patients, pharmacologically and non-pharmacologically. According to the Korean Academy of Asthma, Allergy and Clinical Immunology (KAAACI), the recommendation of AR pharmacotherapy: (1) intranasal corticosteroid (INCS)/intranasal antihistamine (INAH) combination therapy, (2) oral antihistamine/INCS combination therapy, (3) leukotriene receptor antagonist (Yang et al., 2023). Besides, non-pharmacological interventions such as avoidance of triggers or allergens and environmental control.

To date, many studies have been conducted using herbs in treating allergic rhinitis and rhinosinusitis. The most recent systematic review was done regarding herbal medicine in allergic rhinitis in the year 2021 however, the review includes all available herbs that have the potential to treat allergic rhinitis such as *Zingiber Officinale, Psidium Guajava* and *Curcuma Longa* (Koshak, 2021). Despite many studies being done on the effects of NS on rhinosinusitis, there is paucity in the systematic analysis between these studies to draw a firm conclusion on the effects of NS towards rhinosinusitis in terms of optimum therapeutic dose and efficacy compared to anti-histamine or anti-allergic drugs. Moreover, many NS studies showed non-toxic properties and low side effects profile, especially on mast cells (Ikhsan et al., 2018). Hence, the current study was conducted to collect, systematically analyse and conclude the relevant studies on NS effects on rhinosinusitis in humans and animals.

Methods

Protocol

The current systematic review adhered to the statement and overall principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021).

Eligibility criteria

This systematic review examined the effects of NS on treating the rhinosinusitis of human and animal subjects in terms of optimum therapeutic dose, efficacy and safety profile compared to anti-histamine or anti-allergic drugs.

Human model

The study subjects were aged between 18 to 80 years and diagnosed with allergic rhinitis or sinusitis. According to the World Allergy Organization (WAO) 2023, the diagnosis of allergic rhinitis or sinusitis can be determined by the history which is the symptoms and the physical examination such as

skin prick as a confirmatory test. The patients with the symptoms of allergic rhinitis such as sneezing, nasal congestion, rhinorrhoea and positive skin-prick test will specify allergen triggers will be included in this review (Small et al., 2018). The study design included randomized controlled trials (RCT), cohort studies, case-control, case series and quasi-experimental studies are also included in the systematic review. The comparator of the studies was pharmacological interventions such as leukotriene receptor antagonist (LTRA), and montelukast. Full-text original articles published from 2010 until 2023 in the English language were included. However, this systematic review excluded studies that involved pregnant or suspected pregnant women, smokers and alcohol drinkers.

Animal model

On the other hand, the animal inclusion involved in this review includes mammal models that consist of mice, rats and rabbits regardless of gender, age, species or strain. The comparator of the studies was pharmacological interventions such as corticosteroids: mometasone fuorate. Meanwhile, the exclusion criteria included of non-mammal models such as zebrafish, and mammal models that were diagnosed with multiple diseases such as allergic rhinitis with diabetes mellitus rats or diseases besides allergic rhinitis or sinusitis.

Outcome

The outcome in this review was allergic rhinitis symptoms reduction or resolvents such as sneezing, nasal congestion and rhinorrhoea including the safety profile of NS. Moreover, the histological changes or the changes in chemical parameters such as IgE levels, histamine levels and interleukin levels will be included in this systematic review.

Search strategy

Studies or articles were searched from four databases which include Scopus, Cochrane Library, PubMed, and Google Scholar. The search strategy included a combination of domain and sub-domain that were combined with Boolean operators "OR" and "AND". Keywords within the same domain were connected using the Boolean operator "OR" while "AND" operator was used to connect keywords between other domains. The search terms included four main domains from the title of this study in alignment with the inclusion and exclusion criteria which were: (1) effects: list of all keywords that are synonyms to effect such as benefits and advantages; (2) NS and its associated terms; (3) allergic rhinitis: a term describing patients who have been diagnosed with AR or sinusitis or rhinosinusitis; and (4) subjects: human or animal models. The list of keywords that were used for each domain are listed in Table 1. Besides, the snowball technique which is a technique to search for articles from the reference list of articles retrieved from the databases, was also used to add more articles for selection.

Table 1: The keywords used in search of articles from databases

Keywords	Effects	*Nigella Sativa*	Rhinosinusitis	Subjects	
Synonym 1	Effect	*N. Sativa*	AR	Animals	Adults
Synonym 2	Benefit	NS	Allergic patients	Rats	Human
Synonym 3	Benefits	Black seed	Hay fever	Experimental trial	People
Synonym 4	Positive effect	Thymoquinone	Sinusitis	Preclinical trial	Individuals
Synonym 5	Positive effects	Black cumin	Allergic rhinitis	Rabbits	Clinical trial
Synonym 6	Positive impact	Habbatus Sauda	-	Mice	-
Synonym 7	Positive impacts	Habbat-uL-Sauda	-	Rodent	-
Synonym 8	Advantage	-	-	-	-
Synonym 9	Advantages	-	-	-	-

Study records

Data management

All identified studies from the search strategy were retrieved from the databases and kept in separate folders according to each database in the library of the Mendeley reference manager. There was a folder that placed all the identified articles for duplicate checking. Duplicate studies were removed from the folder. Subsequently, the remaining studies were exported as a BibTeX file and converted to an Excel file using a BibTeX format converter for the selection process.

Study selection

Two authors (MNM & MZA) independently examined the studies against predetermined eligibility criteria in the stages of title, abstract, and full-text study selection. None of the

screening authors were blinded to any details of the studies. Two independent authors independently reviewed study titles and abstracts until convergence was reached. In instances of discrepancies, the two authors engaged in discussion, and if consensus was not reached, the disagreements were further deliberated with the involvement of the third author (NAY). Criteria were adjusted as needed during this collaborative process. Articles meeting the inclusion criteria underwent a thorough full-text assessment. If necessary, the authors were contacted to address missing or insufficient information for determining study eligibility. Reasons for article exclusion were documented throughout the study selection process. Microsoft Excel was employed for study selection, and a consolidated list of articles for data extraction was created and stored in Mendeley and Microsoft Excel.

Data collection/extraction

Qualified studies underwent independent review, and pertinent data were extracted. The gathered information encompassed authors, language, publication year, study region, objectives, study design, duration, total participants recruited, intervention, and outcomes: symptom reduction and safety profiles. Data from each study were entered into a table in Microsoft Excel to ease the comparison process between the included studies. Numerical data were also extracted and expressed as mean ± standard deviation, or mean (SEM), and p-values, and the differences were considered statistically significant when $p < 0.05$.

Quality appraisal and the risk of bias assessment

Two authors (MNM & MZA) independently assessed the risk of bias for all included human studies by assessing their methodological quality using the Joanna Briggs Institute (JBI) critical appraisal checklists (Joanna Briggs Institute, 2017). A score of '1' was given if the studies fulfilled the stated criteria of the checklist and '0' if not. After that, the total score was calculated and converted into a percentage. Studies with a percentage of <50% were considered as having a high risk of bias, while moderate risk, and high risk of bias if the percentage were between 50% - 69% and ≥70%, respectively (Franco et al., 2020). The risk of bias results for each study type was visually represented using traffic-light plots through the utilization of Risk-of-bias VISualization (robvis) (McGuinness & Higgins, 2021).

Meanwhile, the quality assessment of all selected animal intervention studies was conducted using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE's) risk of bias tool. It comprised of 10 domains encompassing six types of biases: sequence generation, baseline characteristics, allocation concealment, random housing, researcher blinding, random outcome assessment, outcome assessor blinding, incomplete outcome data, selective outcome reporting, and "other sources of bias".

The risk of bias assessments for both human and animal studies was performed by two independent reviewers (MNM & MZA). When there is a disagreement, the reviewers debate it and reach a resolution based on mutual agreement or appoint a third reviewer (NAY) to resolve that particular disagreement.

Data synthesis

A narrative synthesis was used in this systematic review to describe the qualitative data from each included study. The narrative synthesis provided a written summary of the study's characteristics, study design, population, models of prediabetes that were used, interventions, and comparison studies. The framework method was employed for all parts to examine patterns and organize data according to the subthemes (Bauer, 2013). This method generated a new structure for the data, which made it easier to summarise the data in a manner that can support the research question in this study (Bauer, 2013). Results by subtheme were presented in narrative form to describe the findings of the synthesis.

Results

Study selection

Initially, a total of 360 studies were identified within the databases (PubMed, Scopus, Cochrane Library and Google Scholar). PubMed located 31 studies, Scopus located 124 studies, and Cochrane Library located 173 studies which provided a total of 328 studies. An additional 32 studies were discovered through Google Scholar.

From 360 articles, 41 studies were excluded due to being duplicates, leaving 319 studies to be screened. After manually screening the title and abstract, 298 studies were excluded as (i) they did not have the target outcome which is resolving or reducing allergic rhinitis symptoms (n = 221), (ii) recruited the wrong study population such as children or participants under the of 18 years old (n = 60), and (iii) review articles (n = 17). The remaining study was 21.

Furthermore, 10 out of the remaining 21 studies were excluded as no full-text was available. Eventually, 11 studies were assessed for eligibility and one study was excluded due to recruiting all types of allergic subjects such as skin allergies. Finally, only 10 studies were selected.

In addition, the snowball technique was also employed, resulting in an additional 13 studies. This involved searching for related studies within the references of the previously identified articles in the databases. Three studies were removed as there was no access to the full-text articles, leaving 10 studies. From this, five studies were excluded due to wrong outcomes such as in determining the efficacy and safety of olopatadine/mometasone nasal spray for the treatment of seasonal allergic rhinitis and three studies had the wrong study population which was rhino-conjunctivitis patients, leaving only two studies to be included via the snowball technique.

Consequently, this search approach yielded a total of 12 studies meeting the inclusion criteria and deemed eligible for inclusion in this systematic review, with ten sourced from databases and two from the snowball technique. Figure 1 displays a PRISMA flow diagram illustrating the results from all databases and the process of article selection.

Risk of bias within studies

Risk of bias of the 12 studies are divided into seven human studies (Alsamarai et al., 2014; Ansari et al., 2010; Isik et al., 2010; Nemati et al., 2021; Nikakhlagh et al., 2011; Oysu et al., 2014; Rezaeian and Amoushahi Khouzani, 2018) and five animal studies (Gul et al., 2022; Gunel, 2017; Liao et al., 2021; Yoruk et al., 2017; Yurttas et al., 2016). The seven human studies' risk of bias was assessed using the JBI checklist for Randomized Controlled Trials (RCT). On the other hand, SYRCLE risk of bias tools were adopted for the animal studies.

Based on Figures 2 and 3, six out of 12 human and animal studies (Alsamarai et al., 2014; Ansari et al., 2010; Isik et al., 2010; Nemati et al., 2021; Oysu et al., 2014; Rezaein and Amoushahi Khouzani, 2018) demonstrated low risk of bias (showing high percentage of positive answers to the questions of JBI tool). This is because randomized controlled clinical trials (RCTs) serve as the gold standard for establishing the effectiveness and safety of a treatment. They can illustrate a new treatment's superiority over an established standard treatment or a placebo (Kabisch et al., 2011). Three articles comprised of one human study (Nikakhlagh et al., 2011) and two animal studies (Gunel, 2017; Liao et al., 2021) had a moderate risk of bias. Finally, the three remaining articles (Gul et al., 2022; Yoruk et al., 2017; Yurttas et al., 2016) show a high risk of bias comprising animal studies.

Based on Figure 2 of human studies, there was a high risk of bias for domains four, five and seven (Ansari et al., 2010; Isik et al., 2010; Nikakhlagh et al., 2011; Oysu et al., 2014), due to those delivering treatment and the outcomes assessors were not blinded to the treatment assignment. Initial text deleted – as commented by the reviewer.

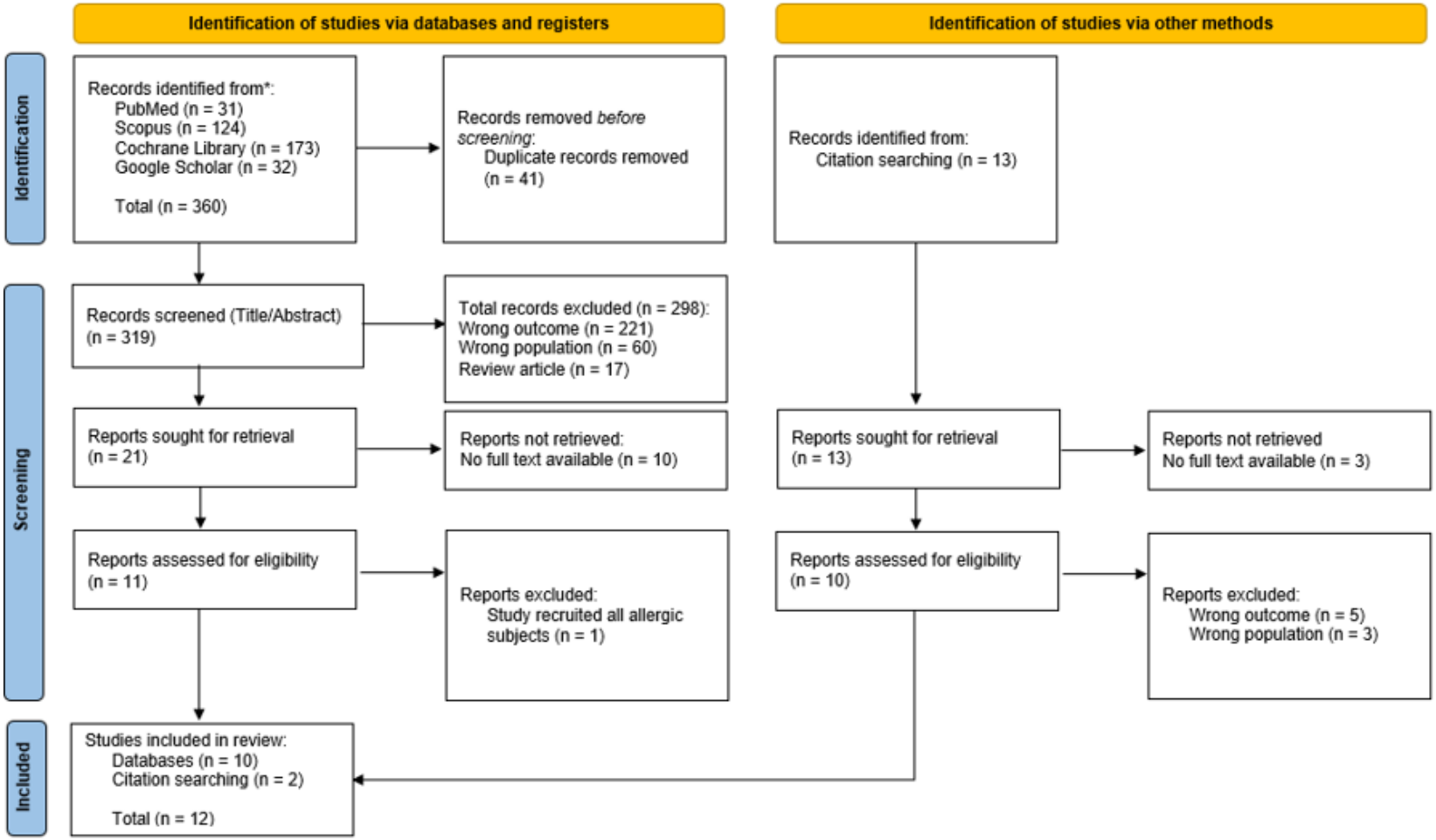

Fig. 1: PRISMA flowchart of the study selection process.

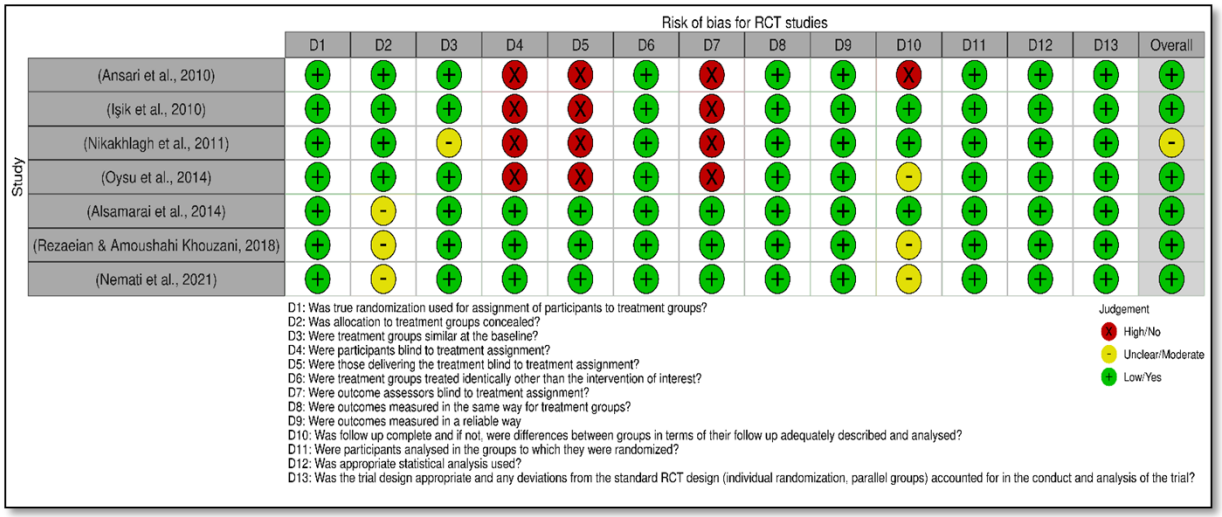

Fig. 2: Risk of bias for RCT studies.

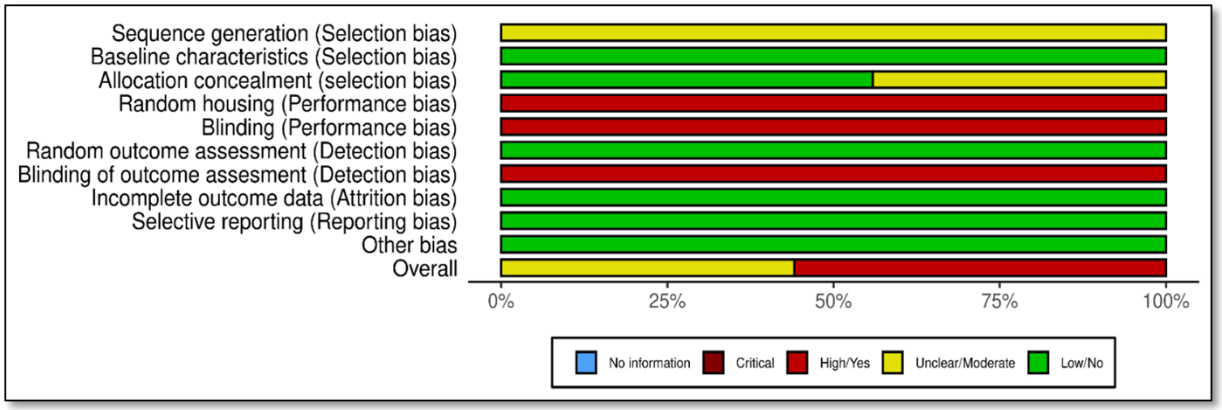

Fig. 3: PRISMA flowchart of the study selection process.

Table 2: Summary of the main characteristics of the seven human studies.

Author, year	Study design	Study region	Participants & Study Duration	Method/ Parameter	Results
(Ansari et al., 2010)	RCT	Nawabshah, Pakistan	**Participants**: 47 seasonal allergic rhinitis patients **Duration**: 2 weeks	**Route of administration**: Oral Comparison of Montelukast with NS (250mg/day) for the treatment of seasonal allergic rhinitis symptoms	• Montelukast and NS reduced the **day-time** and **ophthalmic symptoms** ($P < 0.001$) • NS group reduced in **nocturnal symptoms** at day-7 ($P = 0.001$)
(Işik et al., 2010)	RCT	Istanbul, Turkey	**Participants**: 31 allergic rhinitis patients **Duration**: 2 months	**Route of administration**: Oral Impact of NS seed (2g/day) on symptom levels, peripheral blood polymorphonuclear leukocyte (PMN) functions, and lymphocyte subsets in individuals with allergic rhinitis	• **Phagocytic and intracellular killing activities** of specific immunotherapy (SIT) with NS showed significant increases after one month compared to pre-SIT levels ($P < 0.01$). • **CD8 counts** of patients receiving SIT plus NS significantly increased compared to patients receiving only SIT
(Nikakhlagh et al., 2011)	RCT	Ahwaz, Iran	**Participants**: 66 allergic rhinitis patients **Duration**: 1 month	**Route of administration**: Oral Anti-inflammatory effects of NS oil (0.5mls) in individuals experiencing allergic rhinitis symptoms	**Itching**: • Statistically significant ($P = 0.0014$) between Day 0 & 15 • Statistically significant ($P = 0.001$) between Day 0 & 30 **Nasal congestion**: • Statistically significant ($P = 0.0012$) between Day 0 & 15 • Statistically significant ($P = 0.001$) between Day 0 & 30 **Sneezing**: • Statistically significant ($P = 0.001$) between Day 0 & 15 • Statistically significant ($P = 0.001$) between Day 0 & 30

					Runny nose: • Statistically significant (P = 0.0019) between Day 0 & 15 • Statistically significant (P = 0.001) between Day 0 & 30 **Turbinate hypertrophy and mucosal pallor**: • Statistically significant (P = 0.0012) between Day 0 & 15 • Statistically significant (P = 0.001) between Day 0 & 30 **Mean IgE**: • NS group: 3.31 • Placebo: 15.38 **Mean peripheral blood eosinophil percentage**: • NS group: 0.086 • Placebo: 0.350
(Oysu et al., 2014)	RCT	Istanbul, Turkey	**Participants**: 42 geriatric patients with nasal dryness and associated symptoms **Duration**: 1 month	**Route of administration**: Nasal Impact of topical NS oil on symptoms associated with aging, including nasal dryness, stuffiness, itching, crusting, and burning.	**Mucociliary clearance**: • No significant difference (P > 0.05) **Sinonasal symptoms**: • No significant difference (P>0.01) **Adverse effects**: • 2 patients complained regarding taste and odour of NS oil
(Alsamarai et al., 2014)	RCT	Tikrit, Iraq	**Participants**: 188 patients presenting with mild, moderate and severe allergic rhinitis **Duration**: 6 weeks	**Route of administration**: Nasal Efficacy of NS oil topical application as a treatment patients with allergic rhinitis	**Mild active group**: • Improve at 3rd weeks as 80% (P=0.01) • Improve 100% at 6 weeks (P=0.01) **Moderate active group**: • Improve at the 3rd week (P=0.008), 68.7% • 93.7% at 6 weeks (P=0.002) **Severe active group**: • Improve at 3rd weeks as 58.3% • 83.4% at 6 weeks (P=0.009)

(Rezaeian & Amoushahi Khouzani, 2018)	RCT	Isfahan, Iran	**Participants**: 65 patients diagnosed with rhinosinusitis, clinical symptoms, endoscopic evaluation and CT scan **Duration**: 3 months	**Route of administration**: Nasal Comparison of NS nasal spray and sodium chloride nasal spray in the management of patients with Chronic Rhinosinusitis Without a Nasal Polyp (CRSsNP)	• 8 weeks of interventions, the Lund–McKay, Modified Lund Kennedy, and SNOT-22 scores in the intervention group were significantly lower compared to the placebo group (P < 0.0001)
(Nemati et al., 2021)	RCT	Tehran, Iran	Participants: 50 chronic rhinosinusitis patients Duration: 28 days	**Route of administration**: Nasal Impact of Nigella seed oil on chronic rhinosinusitis (CRS) symptoms	**Mean SNOT-22 score**: • NS group: 19.08 ± 13.21 • Placebo group: 37.15 ± 21.47 (P = 0.001) **Major symptoms**: • Pain or pressure in the face (P = 0.011) • Congestion or fullness in the face (P = 0.028) • Congestion or nasal obstruction (P = 0.025) • Pus or nasal discharge (P = 0.032), between days 0 and 28 in the drug and placebo groups **Endoscopic nasal examination**: **NS group**: • Mild inflammation/muco-purulent discharge in 9 cases (37.5%) • Grade 1 polyposis in 6 patients (25%) **Placebo group**: • Inflammation/muco-purulent discharge in 14 subjects (53.8%) • Grade 1 nasal polyposis in 12 cases (46.1%) **No adverse effects**

Table 3: Summary of the main characteristics of the five animal studies.

Author, year	Study design	Study region	Type, total subjects & study duration	Method/ Parameter	Results
(Gul et al., 2022)	Case control	Istanbul, Turkey	**Animal type**: Rat **Total subjects**: 28 Wistar Hannover rats weighing 250-350 g, two to four months old **Duration**: 28 days	**Route of administration**: Nasal Comparison of mometasone furoate and NS oil in the prevention of disease symptoms in a rat AR model	Number of **sneezing**: • Day 14 (P = 0.000) than Day 1 • Day 17 (P = 0.012) than Day 14 • Day 20 (P = 0.001) than Day 14 • Day 23 (P = 0.001) than Day 14 • Day 26 (P = 0.001) than Day 14 • Day 28 (P = 0.001) than Day 14 **Nose scratching** frequency: • Day 14 (P = 0.001) than Day 1 • Day 17 (P = 0.001) than Day 1 • Day 20 (P = 0.001) than Day 1 • Day 23 (P = 0.002) than Day 1 • Day 26 (P = 0.002) than Day 1 • Day 28 (P = 0.001) than Day 1 Histology Evaluation**:** **Mild inflammation**: • 14.3% of the control group, AR group and NS oil group • 28.6% in mometasone furoate group **Loss cilia**: • NS group: 71.4% • Control % mometasone furoate group: No loss **Increase Goblet cells**: • Control group: 71.4%

					• Mometasone furoate group: 42.9% • NS group: 14.3% and did not have vascular proliferation
(Günel, 2017)	Case control	Aydin, Turkey	**Animal type**: Rat **Total subjects**: 42 of 12-15 month-old female Wistar rats **Duration**: 2 weeks	**Route of administration**: IV Effect of TQ on airway inflammation in a rat model of AR	**OVA-specific IgE levels**: • TQ10+AR group: (P = 0.038) • CS+AR groups: (P = 0.048) **IL-4 levels**: • TQ at dose of 3 mg/kg and 10 mg/kg: (both, P = 0.013) **IFN-g**: • Not differ significantly among the AR, control and treatment groups, its production tended to decrease in treatment groups **IL-10**: • 3 mg/kg TQ group (P = 0.033) • 10 mg/kg TQ group (P = 0.002) **Eosinophil count**: • TQ3+AR group: (P = 0.002) • TQ10+AR group: (P = 0.013) **Edema**: • TQ at doses of 3 mg/kg and 10 mg/kg: (both, P < 0.001) **TNF-a**: • CS+AR group: (P = 0.05) • TQ3+AR group: (P = 0.0015) • TQ10+AR groups: (P = 0.004) **IL-1b**: • CS+AR group: (P < 0.001) • TQ10+AR groups (P = 0.006)

					• TQ at dose of 3 mg/kg had no effect (P = 0.072)
(Yurttaş et al., 2016)	Case control	Bolu, Turkey	**Animal type**: Rabbit **Total subjects**: 24 male New Zealand rabbits (2,000–3,000 g each; 20–24 weeks **Duration**: 7 months	**Route of administration**: Nasal Histopathological effects of TQ treatment of allergic rhinitis rabbit model compared to nasal mometasone furoate	**Nasal mucosa**: • Control group: Normal • Ovalbumin (OVA) sensitization group: Elevated counts of inflammatory cells. Intraepithelial goblet cell hypertrophy and hyperplasia. Vascular congestion and ciliary loss • TQ group: The counts of intraepithelial and submucosal inflammatory cells were markedly lower than in the OVA group (P < 0.001). Reduction in the number and intensity of hypertrophic goblet cells • Mometasone furoate group: histological structure was slight irregularities, there were significant improvements compared to the OVA group. • Inflammation status of the mometasone furoate and TQ groups, the counts of intraepithelial and submucosal inflammatory cells were similar (P = 0.608) **TUNEL assay**: • Not differ between the mometasone furoate and TQ groups • TUNEL-positive cell counts similar

(Liao et al., 2021)	Case control	Shanghai, China	**Animal type**: Mice **Total subjects**: 72 specific pathogen-free five-week-old BALB/c male mice **Duration**: 28 days	**Route of administration**: Oral Anti-allergenic effects of the aqueous extract of BLAB (in a specific proportion) on the ovalbumin (OVA)-induced allergic rhinitis (AR) model.	**Nasal symptoms**: • Aqueous extract of BLAB group: Reduced the nasal symptoms compared to the OVA group • Dex group: Significant inhibition of nasal symptoms **Inflammatory cells**: • Decreased in nasal lavage fluid (NALF) in the BLAB and BLAB 200 and BLAB 400 group **Thickness of nasal mucosa**: • Aqueous extract of BLAB and Dex: Reduced the infiltration of inflammatory cells into the nasal mucosa **Levels of histamine, total IgE and OVA-specific immunoglobulins in serum**: • Administration of the aqueous extract of BLAB decreased the levels of histamine, total IgE, OVA-specific IgE, and OVA-specific IgG1 in serum, especially at a dose of 400 mg/kg
(Yoruk et al., 2017)	Case control	Erzurum, Turkey	**Animal type**: Rabbit **Total subjects**: 30 adult male albino rabbits weighing an average of 3 kg **Duration**: 1 week	**Route of administration**: Oral Effects of three different doses of oral administration of NS in a rabbit model of rhinosinusitis, compared with cephalexin treatment	**Histopathological lesions:** **Numerical density of neutrophils**: • Control group: 0.000351/µm3 • Cephalexin group: 0.000020/µm3 • NS 50 mg/kg/d group: 0.000072/µm3 • NS 100 mg/kg/d group: 0.000058/µm3

					• NS 200 mg/kg/d: 0.000068/µm3 **Nitric oxide (NO) level**: • Control group: Increased in the saline treated group in comparison to the cephalexin 20 mg/kg/d, NS 50 mg/kg/d, NS 100 mg/kg/d and NS200 mg/kg/d groups. **Mean tissue total NO levels**: • Significantly ($P < 0.001$) higher in the control group and correlated well with disease acuteness • Cephalexin group: 163.31 µmol/ ml • NS 50 mg/kg/d: 166.40 µmol/ml • NS 100 mg/kg/d: 165.20 µmol/ml • NS 200 mg/kg/d: 166.43 µmol/ml • Control group: 184.17 µmol/ml

On the other hand, three out of five animal studies had a high risk of bias meanwhile, the other two showed moderate risk of bias. All animal studies included in this review show a high risk of performance bias and detection bias (blinding outcome assessment), the individuals administering treatment and evaluating study outcomes were aware of the assigned treatments. For random housing, rats (Gul et al., 2022; Gunel, 2017), rabbits (Yurttas et al., 2016) and mice (Liao et al., 2021) were kept in room temperature conditions for 12 hours in light/dark cycle conditions.

Study characteristics

All studies were published between the years 2010 and 2022 and comprised seven studies involving the human population that consisted of RCT (n = 7) and five studies involving the animal population that consisting of rats (n = 2), mice (n = 1) and rabbits (n = 2).

For human studies, Table 2 shows three studies conducted in Iran (Nemati et al., 2021; Nikakhlagh et al., 2011; Razaeian and Amoushahi Khouzani, 2018), two in Turkey (Isik et al., 2010; Oysu et al., 2014), one in Pakistan (Ansari et al., 2010) and one in Iraq (Alsamarai et al., 2014). Five studies recruited patients diagnosed with allergic rhinitis (Alsamarai et al., 2014; Ansari et al., 2010; Isik et al., 2010; Nikakhlagh et al., 2011; Oysu et al., 2014) meanwhile two studies recruited patients with chronic rhinosinusitis regardless of genders (Nemati et al., 2021; Razaeian and Amoushahi Khouzani, 2018). The study conducted by Ansari et al. (2010) mainly focuses on the comparison of the Leukotriene receptor antagonist, Montelukast with NS in resolving or reduction of allergic rhinitis symptoms. On the other hand, four studies mainly focus on the efficacy of NS in reducing symptoms without comparing it to other medications or interventions (Alsamarai et al., 2014; Işik et al., 2010; Nikakhlagh et al., 2011; Oysu et al., 2014). Furthermore, the study conducted by Alsamarai et al. (2014) divided the participants into stages of allergic rhinitis symptoms such as mild, moderate and severe groups. Hence, the optimum efficacy of NS can be identified in which stage of allergic rhinitis.

Moreover, two studies focus on chronic rhinosinusitis (CR) that represent their data with Sinonasal Outcome Test 22 (SNOT-22) (Nemati et al., 2021; Rezaeian & Amoushahi Khouzani, 2018). The SNOT-22 serves as a validated self-administered survey designed for evaluating individuals with chronic rhinosinusitis (CRS). Comprising 22 items, respondents rate each item on a scale from 0 ('no problem at all') to 5 ('worst possible symptom'). Total scores on the SNOT-22 can vary from 0 to 110, with elevated scores reflecting more severe symptoms.

Subsequently, the results of animal studies are presented in Table 3. There were four studies conducted in Turkey (Gul et al., 2022; Gunel, 2017; Yoruk et al., 2017; Yurttas et al., 2016) and one in China (Liao et al., 2021). Out of these five animal studies, three mainly focus on the comparison of corticosteroids with NS. Two of the studies used topical corticosteroid, which was mometasone furoate (Gut et al., 2022; Yurttas et al., 2016) and one study used IV dexamethasone as an intervention (Günel, 2017). Finally, the remaining two studies utilized different doses of NS preparation without comparing them with any medication (Gunel, 2017; Yoruk et al., 2017). Hence, these two studies proposed the suggested dose which would eventually lead to the optimum doses in treating rhinosinusitis symptoms.

Individual outcomes of the studies

The targeted outcomes for this review are allergic rhinitis symptoms reduction or resolvent which include sneezing, nasal congestion and rhinorrhoea. In addition, the safety profile of NS was included if stated in the study. Further, the histological changes or the changes in chemical parameters such as IgE levels, histamine levels and interleukin levels were also included especially in animal studies.

Symptom reduction

Based on Tables 2 and 3, seven out of 12 studies emphasized the symptom reduction of allergic rhinitis (Alsamarai et al., 2014; Ansari et al., 2010; Gul et al., 2022; Liao et al., 2021; Nikakhlagh et al., 2011; Oysu et al., 2014) and chronic rhinosinusitis (CRS) (Nemati et al., 2021).

Six studies show positive effects in terms of symptom reduction such as sneezing (Gul et al., 2022; Liao et al., 2021; Nikakhlagh et al., 2011), day-time symptoms (Ansari et al., 2010) and major symptoms of CRS such as pressure in the face or nasal obstruction (Nemati et al., 2021). Moreover, NS could completely resolve mild allergic rhinitis symptoms ($P = 0.01$) and reduce as much as 83.4% after 6 weeks of treatment ($P = 0.009$) (Alsamarai et al., 2014). However, a study by Oysu et al. (2014) revealed that although the symptoms were reduced at the individual level, but when compared between

the NS group and the ISCS (isotonic sodium chloride solution) group, there was no significant difference in the nasal mucociliary clearance ($P > 0.05$) and sinonasal symptoms ($P > 0.01$).

Histological changes

Based on Table 3, mild inflammation was detected in 14.3% of rats within the control group, the allergic rhinitis (AR) group, and the NS oil group. In contrast, the mometasone furoate group exhibited a higher incidence of mild inflammation, with 28.6% of rats showing such levels (Gul et al., 2022). In addition, the hypertrophic goblet cells exhibited a notable reduction in intensity and quantity in the TQ group (Yurttaş et al., 2016). Plus, the numerical density of neutrophils in NS groups also exhibits better results than the control group as the dose of 100 mg/kg/d NS shows 0.000058/μm3 and 200 mg/kg/d NS shows 0.000068/μm3 (Yoruk et al., 2017).

Chemical parameter

The CS+AR, TQ3+AR, and TQ10+AR groups showed a significant decrease in TNF-α expression ($p=0.05$, $p=0.015$, $p=0.004$, respectively). Conversely, OVA (ovalbumin-induced AR) sensitization led to a notable increase in both TNF-α and IL-1β expression levels (both, $p<0.001$) (Günel, 2017). Furthermore, administering the aqueous extract of BLAB (black cumin seeds, liquorice, anise seeds, black tea) orally resulted in a significant dose-dependent decrease in IL-4, IL-5, and IL-13 levels in both nasal mucosa and serum compared to the OVA group. Conversely, there was a noteworthy and dose-independent rise in IFN-γ, IL-12, and IL-10 levels in both nasal mucosa and serum of mice in the BLAB group, as opposed to the OVA group (Liao et al., 2021).

Comparison with anti-allergic medication

The statistical analysis indicated that the impact of both montelukast and NS in reducing daytime symptoms was highly significant ($P < 0.001$) when compared with the baseline pre-treatment phase of the study (Ansari et al., 2010). However, upon comparing the inflammation status between the mometasone furoate, and the TQ group which is the main active ingredient of NS, it was observed that the intraepithelial and submucosal inflammatory cell numbers were similar ($P = 0.608$) (Yurttaş et al., 2016).

Discussion

This study was conducted to systematically review the effects of NS (black seed) on rhinosinusitis in both humans and animals. To comprehend the effects of NS in rhinosinusitis, understanding the pathophysiology of allergic rhinitis and rhinosinusitis is crucial. Many researchers have performed experimental studies on NS, recognizing it as a potent herb for treating various ailments. In recent decades, there has been significant exploration of NS's pharmacological actions, particularly for rhinosinusitis treatment.

NS demonstrates positive effects on reducing symptoms of allergic rhinitis and rhinosinusitis, with itching and sneezing serving as a benchmark for efficacy in allergic rhinitis. In one clinical study, the frequency of sneezing significantly decreased between Day 0 and Day 30 ($P = 0.001$) for the treatment group consuming oral 0.5ml NS oil in 66 allergic rhinitis patients within a one-month duration (Nikakhlagh et al., 2011). An earlier study by Ansari et al. (2010) in line with these findings, noted a significant reduction in daytime symptoms, including sneezing, between Day 0 and Day 14 ($P < 0.001$) in 47 seasonal allergic rhinitis patients. However, the categorisation of symptoms between these two studies is different, where Nikakhlagh et al. (2011), categorised symptom severity into stages (mild, moderate, severe), while Ansari et al. (2010), provided a general assessment of symptom severity.

However, in geriatric patients, there was no significant difference in the reduction of sinonasal symptoms such as itching ($P = 0.083$). This could be due to the process of ageing, which leads to the gradual replacement of lymphatic tissue in the nasal mucosa with connective tissue, causing fibrosis and interfering with mucosal secretory function (Oysu et al., 2014). Furthermore, this phenomenon may be attributed to the impact of osmolarity and tonicity which influence ciliary beat frequency. Research has demonstrated that isotonic and hypotonic solutions do not induce ciliary slowing (Oysu et al., 2014). Hence, a hypertonic solution of NS might be employed for administration in the elderly. Moreover, mucociliary transport rates tend to decline with ageing (Bailey, 2022). As a result, the optimised effectiveness of NS may be compromised. Furthermore, this study did not specifically elucidate the effects of NS on allergic rhinitis in geriatric patients. While NS demonstrates promising potential in reducing symptoms through

its anti-inflammatory effects, it is a noteworthy candidate for the treatment of allergic rhinitis and rhinosinusitis and, thus needs further exploration in geriatric populations.

Recent studies on rhinosinusitis conducted in Iran (Nemati et al., 2021; Rezaeian & Amoushahi Khouzani, 2018) revealed promising results on the NS within one-month to 3 months durations. In 50 adult chronic rhinosinusitis patients, there is a notable clinical improvement in nasal obstruction ($P = 0.025$), nasal discharge ($P = 0.032$) and pain or pressure on the face ($P = 0.011$) between days 0 and 28 in the NS nasal drop compared to placebo groups (Nemati et al., 2021). This suggests the anti-inflammatory and analgesic properties of NS exhibiting its effects. In addition, the mean SNOT-22 score of the NS group was 19.08 ± 13.21 significantly lower ($P = 0.001$) compared to the placebo group (37.15 ± 21.47). In another study, 65 adult chronic rhinosinusitis patients showed a very significant reduction in Lund-McKay, Modified Lund Kennedy and SNOT-22 scores in the NS nasal spray group compared to the placebo group ($P < 0.0001$) (Rezaeian & Amoushahi Khouzani, 2018). Although both were using SNOT-22 scores, the latter study revealed a more significant outcome, probably due to the study population that excluded rhinosinusitis patients with nasal polyps compared to Nemati et al. (2021) subjects with nasal polyposis stage 1. This could be due to alterations in the anatomical structure of the nasal passages that may impede the optimal efficacy of intra-nasal NS in treating chronic rhinosinusitis.

In animal studies, the symptoms of allergic rhinitis in NS-treated rats exhibit a significant reduction of sneezing ($P = 0.001$) up to Day 28 compared to the allergic rhinitis (AR) group (Gul et al., 2022). Moreover, Liao et al. (2021) emphasized a significant reduction of nasal symptoms such as sneezing and rubbing compared to the ovalbumin (OVA)-induced AR model of the mice group. However, Gul et al. (2022) demonstrated more significant outcomes with nasal administration compared to Liao et al. (2021) which utilised oral administration of NS ($P < 0.01$). Nasal absorption is faster than oral administration since the turbinates of the nasal have extensive surface area and thin membranes, expediting swift absorption into the bloodstream upon contact with a drug (Ehrick et al., 2013).

Histologically, a substantial decrease in eosinophil infiltration, cilia loss, chondrocyte hypertrophy, vascular proliferation, and an elevation in goblet cells was observed in both the mometasone furoate and NS groups compared to the AR group (Gul et al., 2022). There was a statistically significant decrease in neutrophil numbers in both treatment groups when compared to the saline-treated group in 30 adult male rabbits (Yoruk et al., 2017). This study conducted a comparison between NS and cephalexin, with the latter aiming to eliminate infection and mitigate inflammation. It is also worth noting that the positive outcomes of both NS-treated and medication-treated (mometasone furoate and cephalexin) groups are comparable. These studies exhibit the efficacy of NS in terms of its anti-inflammatory, antioxidant and anti-microbial properties.

Subsequently, when analysing the effects of NS on chemical parameters, 10 mg/kg of TQ administered to allergic rhinitis rats had a greater impact on eosinophil count ($P = 0.013$), oedema ($P < 0.001$), and IL-4 ($P = 0.013$) level compared to corticosteroids and 3 mg/kg TQ (Günel, 2017). Moreover, in allergic rhinitis rabbits, 100 mg/kg/day of NS shows a slightly better reduction of nitric oxide (NO) level compared to 50 mg/kg/d and 200 mg/kg/d NS, although all posed significant results compared with the control (Yoruk et al., 2017). Therefore, it is suggested the optimal dosage range for allergic rhinitis and rhinosinusitis treatment, is proposed to be between 10 - 100 mg/kg/day in animal studies. Subsequently, further clinical trials are essential for translational study, as the existing studies have a limited number of RCTs to date, with different study designs and parameters evaluated, with the oral administration of NS ranging from 0.5mls to 250mg to 2g per day. In comparison, there has been a notable p-value significance in many recent animal studies, weighing more on animal research than human studies.

Finally, the extracts from NS seeds and their bioactive components are generally recognised as substances with low toxicity, demonstrating a broad margin of safety (Mashayekhi-Sardoo et al., 2020). Numerous clinical trials exploring NS and TQ have reported the safety of these agents (Mekhemar et al., 2020). There was no significant difference observed in the activities of liver markers (ALT, AST, ALP) and kidney function markers (serum creatinine, serum urea) in healthy adults consuming NS oil formulation containing 5.2% TQ in 200mg per day for 90 days (Thomas et al., 2022). However, it is noteworthy that some adverse effects, including bloating,

nausea, and a burning sensation, were observed in functionally dyspeptic patients treated with NS oil (Tavakkoli et al., 2017). Therefore, it is proposed that NS exhibits a favourable safety profile compared to other herbal plants such as kratom, which can lead to withdrawal and dependence by affecting the central nervous system (CNS) (Prevete et al., 2022).

Conclusion

NS has demonstrated benefits in subjects with rhinosinusitis, including both humans and animals. With the comprehensive data searching and collection, the study has successfully achieved its objective by demonstrating that NS exhibits anti-inflammatory, anti-histaminic, and antimicrobial effects, contributing to the resolution or reduction of symptoms in allergic rhinitis and rhinosinusitis. Furthermore, NS could serve as an alternative treatment to conventional medications like montelukast, mometasone furoate, and dexamethasone since it exhibits a low side effects profile. The recommended optimal dose for the treatment of allergic rhinitis is suggested to be within the range of 10 to 100 mg/kg/day of NS. However, it is important to note that this suggestion is currently limited to animal studies. For human studies, the authors have not concluded the optimum dosage of NS due to different study settings in design and parameters in the clinical trials available. Further investigations are necessary for larger human studies in a standardised method to determine the precise optimum therapeutic dose for the treatment of rhinosinusitis. Finally, the efficacy of NS is proposed to be tested in the rhinosinusitis Malaysian population as part of the SEA area, as there is paucity in the studies conducted in this specific demographic location.

Authors contributions

Conceptualization, N.A. and S.Z.; introduction, M.N. and N.A.; methodology, M.N. and S.Z.; results, M.N., M.Z., N.A. and S.Z.; discussion, M.N. and N.A.; conclusion, M.N. and N.A. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no financial interests or commercial associations.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used Grammarly and ChatGPT to improve readability and language.

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