Traditional herbal medicine in the treatment of acute and chronic rhinosinusitis: a systematic review

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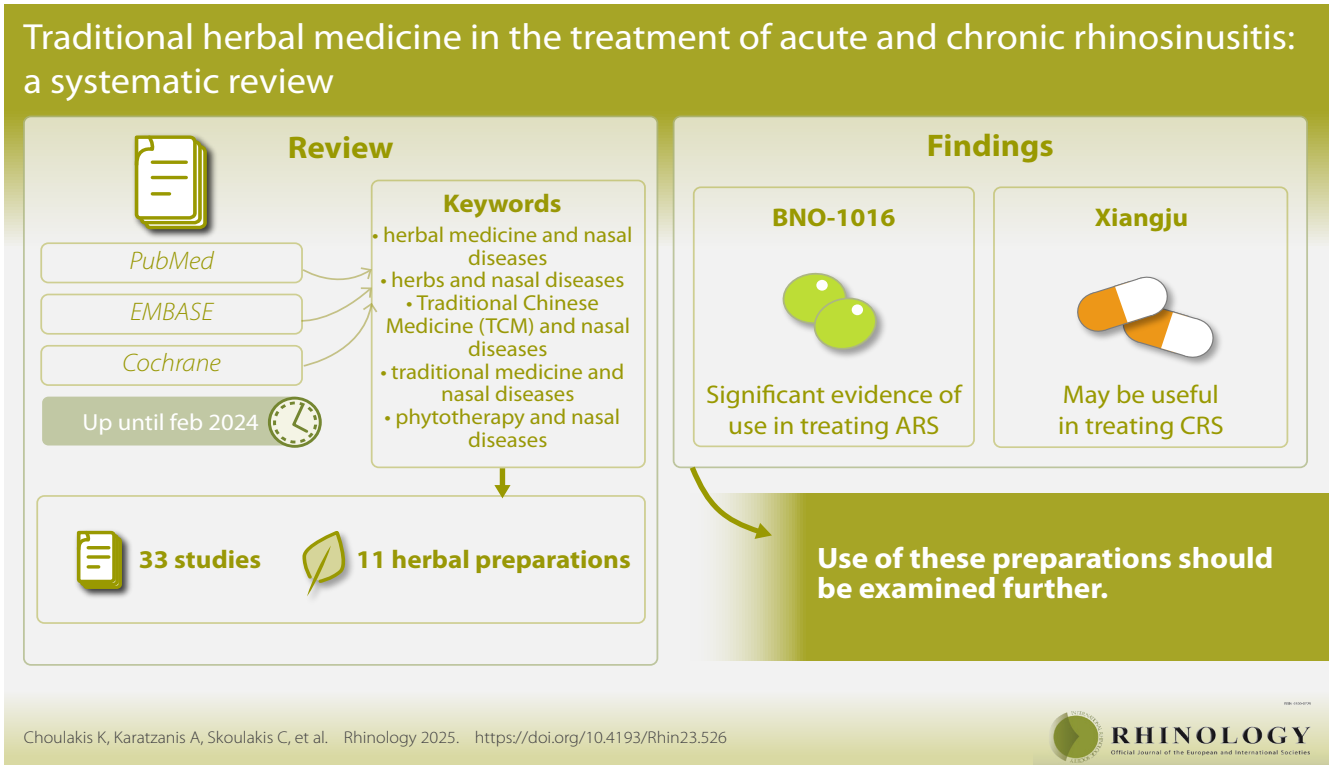
Rhinology 63: 3, 0 - 0, 2025
https://doi.org/10.4193/Rhin23.526



Abstract

Background: Traditional medicine and herbal medicine are relatively commonly utilized by patients for the treatment of acute (ARS) and chronic rhinosinusitis (CRS).

The aim of this study is to review the literature to evaluate scientific evidence regarding the use of herbal preparations in the treatment of rhinosinusitis.

Methodology: We reviewed all published studies until February 2024 in PubMed, EMBASE, and Cochrane, using the following keywords: herbal medicine and nasal diseases, herbs and nasal diseases, Traditional Chinese Medicine (TCM) and nasal diseases, traditional medicine and nasal diseases, phytotherapy and nasal diseases.

Results: Thirty-three clinical studies met the purpose of this review and were assessed. These studies examine the effect of eleven herbal preparations for the treatment of ARS and CRS.

Conclusions: Herbal preparation BNO-1016 presents significant evidence in the literature regarding its use in the treatment of ARS, while the TCM preparation Xiangju might be a useful component in the treatment of CRS. Specific traditional herbal medicinal products, therefore, show promising results for the treatment of rhinosinusitis, and their use should be examined further. Given the relatively high demand for medicinal herbs, therapeutic use of those preparations should be explored further.

Key words: herbal medicine, rhinosinusitis, traditional medicine

Introduction

According to the World Health Organization, traditional medicine is the sum of the knowledge, skill, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement, or treatment of physical and mental illness [1].

Traditional medicine has been partly reintroduced nowadays to the range of therapies a patient might choose to follow. In 2007, 40% of American adult ENT patients utilized at least one alternative form of medical practice [2], while in the UK this percentage reached 41.1% of the population [3]. It is estimated that 60-70% of these patients may not discuss the use of alternative practices with their ENT physician [4]. Moreover, in the latest EPOS version, herbal medicine has been included as an alternative treatment for self and primary care of ARS [5]. There seems to be, therefore, an increased interest in alternative practices, but questions arise regarding evidence to support the use of such practices. The aim of this study is to search for evidence in the literature for the most common herbal preparations and the investigation of their effects in the treatment of acute and chronic rhinosinusitis. Although many types of traditional practices exist, including aromatherapy, acupuncture, etc., this study specifically focuses on herbal preparations.

Materials and methods

The objective of this review is to identify literature evidence that supports or opposes the use of traditional herbal preparation for the treatment of ARS and CRS.

Inclusion and exclusion criteria

The following inclusion criteria were used: clinical studies (metanalyses, systematic reviews, randomized controlled trials [RCTs], cohorts) examining the effects of herbal preparations on ARS and CRS were included in the study. The articles written in a language other than English were excluded only if the abstract was not in English. Otherwise, the non-English articles were translated by a multilingual neural machine translation service and included as well. The final search was updated on the 2nd of February 2024. All studies published until that day were examined.

Identification of studies

We conducted keyword searches in the biomedical electronic databases PubMed, EMBASE, and Cochrane. Searched terms include "Herbal medicine and nasal diseases", "herbs and nasal diseases", "Traditional Chinese Medicine (TCM) and nasal diseases", "traditional medicine and nasal diseases", "phytotherapy and nasal diseases". Manual checks of the references of every study were performed, and related studies, which were unidentified from the primary literature research, were included as well.

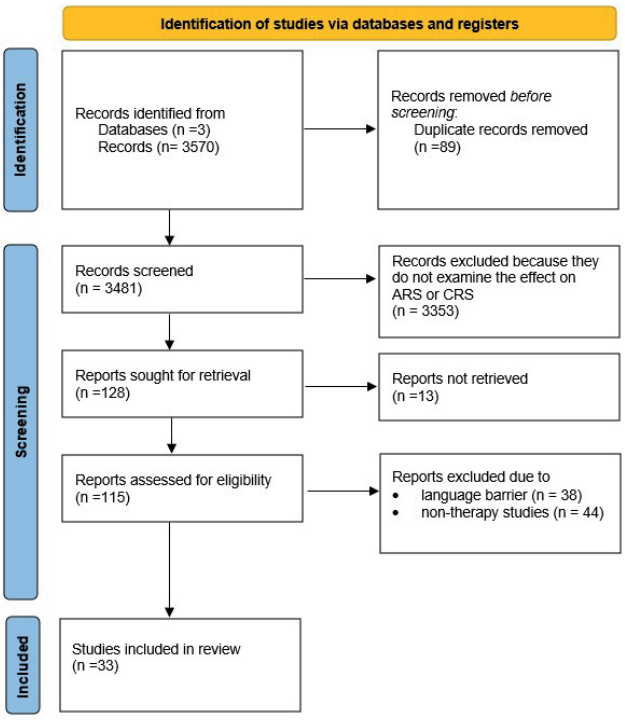


Figure 1. Prisma flow diagram, identification of studies via databases and registers.

Individual herbal preparations that have been identified in the primary research were used as keywords, and the resulting articles were included as well. Duplicates were manually removed. The articles were reported according to the Prisma Guidelines (Figure 1).

The individual characteristics of each study are presented in Table 2, including information such as the names of the authors, the disease and the sample for which these herbal products have been examined, the formulation used, as well as results and conclusions by the authors. A summary of critical appraisal of the studies is also presented in Table 2.

Critical evaluation of studies

Evaluation of each randomized controlled and cohort study was performed utilizing the criteria depicted in Table 1. Each study was classified according to the risk of bias as shown in Table 3. The risk of bias assessment of each study was performed by a single reviewer and was not blinded. For the evaluation of the sum of evidence for each herbal product, we attempted to divide them according to the quality of supporting literature (Table 4). We consider that a meta-analysis and a systematic review that support the use of an herbal drug are high-quality evidence. At least one randomized controlled trial (RCT) with a low or moderately low risk of bias or a well-designed cohort were considered as moderate quality of evidence, and studies other than the aforementioned were considered as low quality of evidence. If inconsistent results were presented among stu-

Table1. Criteria for evaluation of the risk of bias.

Risk of Bias	Study Design	Criteria
Low	RCT	Random sequence generation Allocation concealment Intent-to-treat analysis Blind or independent assessment for important outcomes Co-interventions applied equally Follow up rate >80% Adequate sample size
Moderately low risk	Moderate or poor quality RCT Good quality cohort	Violation of one of the criteria for good quality RCT Blind or independent assessment in a prospective study, or use of reliable data in a retrospective study Co-interventions applied equally Follow up rate of 80%+ Adequate sample size Controlling for possible confounding
Moderately high risk	Moderate or poor-quality cohort Case-control	Violation of any of the criteria for good quality cohort Any case-control design
High risk	Case Series	Any case series design

dies, then these specific herbal drugs were considered to hold a low quality of evidence.

Results

Thirty-three studies met the purpose of this review and were analyzed. These articles examine the effect of eleven herbal preparations against ARS and CRS. The results of the clinical therapy studies were combined in an evidence table (Table 2).

Pimpinella anisum, known as anise, is a spice plant endemic to the eastern Mediterranean region and southwest Asia. It has been studied for its use in chronic rhinosinusitis without polyps. A study conducted by Teheran University Institute compares the efficacy of intranasal Sinupim® (a solution containing Pimpinella anisum) drops with fluticasone intranasal spray in a group of forty-eight patients divided appropriately [6]. The sample size, as mentioned by the researchers themselves, is limited but adequate, and the study is not blinded on the patient side, possibly affecting the credibility of this trial. The two groups were treated for four weeks, which could be considered a short course of treatment, especially in the evaluation of CRS, which presents a long course characterized by exacerbations and periods of remission. In addition, the preparation of the test drops (Sinupim®) is empirical, and the concentration of active substances in the test formulation was not clearly standardized, affecting the efficacy of different test bottles.

Chamomile (*Matricaria chamomilla*) is the common name for several daisy-like plants that belong to the family of Asteraceae. The most common type used therapeutically is chamomile. The therapeutic effect of chamomile against CRS has been evaluated by the double-blind placebo-controlled study of Nemati et al. [7]. The main limitation of this study is that it examines the effect of chamomile on CRS patients without polyps and mild CRSwNP. CRSwNP and CRSsNP exhibit a completely different pathophysiologic sequence [5], which might be affected variably by the testing formulation and should be evaluated separately. The small sample size, the lack of power analysis justification, and the short treatment course affect the robustness of the results as mentioned above.

Ecballium elaterium or squirting cucumber belongs to the Cucurbitaceae family, and it is a relative species of cucumber, watermelon, and zucchini plants. Its juice contains cucurbitacin B, which has anti-inflammatory properties [8], reduces fibrosis and inflammation of nasal mucosa in animals with ARS [9], and presents an anti-microbial effect against MRSA, MSSA, and *C. albicans* [10]. On the other hand, there are a lot of case studies that present the adverse effects of intranasal administration of *Ecballium elaterium* for the treatment of CRSwNP. Most of these studies describe inflammation of the airway passages with oedema of the uvula, that in serious cases even caused hypoxemia [11–16]. There is a study by Sezik et al. in 1995 that studied the effects of *Ecballium elaterium* in 69 patients with sinusitis [17]. The methodology of this study could not be identified. The article uses the term sinusitis, which is a term that might refer to ARS or CRS. The article supports that a cure was succeeded in 91% of patients, which might be realistic only in ARS patients. There is no standard treatment until today that can promise a 91% cure rate in CRS. Further clarification on this subject is needed.

Cyclamen europaeum is a flowering plant endemic to central Europe and the Mediterranean basin. The use of its essential oil has been shown to be safe in a series of preclinical studies in vitro and in vivo. A study by Fernández-Campos et al. showed that saponins, active substances in Cyclamen, do not infiltrate through the nasal mucosa into the systemic circulation when they are administered intranasally [18]. A meta-analysis by Tresti-

oreanu et al. in 2018 showed that *C. europaeum*'s plant extract has a relatively safe profile with a high level of confidence, but as the authors commented, conclusions could not be drawn regarding the efficacy due to the poor methodology of the researched studies [19]. PROSINUS study suggested that intranasal administration of cyclamen extract as monotherapy against ARS has better results than other common therapies without any additional cost [20]. The evidence provided presents a low level of confidence due to its design (observational descriptive study) and possible confounding factors existing due to the different combinations of drugs and other monotherapies that have been compared to *C. europaeum*. In a multicentric randomized study by Kriukov et al., the use of cyclamen is supported as monotherapy against ARS [21]. Ovchinnikov et al.'s study compares the addition of *C. europaeum* to the standard therapy with the standard therapy alone in the treatment of ARS [22]. The main limitation of both studies (Kriukov et al. and Ovchinnikov et al.) is that the combined interventions were used in the control group that differed from the intervention group, which clearly could affect the result. Ovchinnikov et al.'s study contains only a small number of participants, and consequently, conclusions could not be derived safely. There is only one study until now that examines the use of *C. europaeum* against acute exacerbations in CRS. Lopatin et al. compared the efficacy on acute exacerbations in CRS (AECR) between *C. europaeum* with antibiotic, *C. europaeum* monotherapy, and antibiotic alone [23]. This study possibly includes an appropriate number of participants (n=317)—no power analysis was included, but it presents several limitations. The treatment allocation was not randomized but was based upon the treating physician's choice, resulting in a potential selection bias in which people with more severe symptoms would receive the combined treatment. Moreover, the study was not blinded neither to the doctors' side nor the patients' side.

Pelargonium sidoides is endemic to South Africa. The root of this plant was used traditionally in this area as a remedy against upper respiratory tract infections. A double-blind randomized controlled study by Bachert et al. compares the extract of *P. sidoides* with placebo in the treatment of ARS [24]. The main limitation of this study is that the diagnosis of ABRS was presumed, and the diagnostic criteria do not precisely match those of the EPOS2020 [5]. In 2020, Perić et al. compared the efficacy (symptoms, endoscopy, cultures) of pelargonium with the efficacy of amoxicillin in the treatment of uncomplicated bacterial rhinosinusitis [25]. A year later, Perić et al. compared the effects of *P. sidoides* and roxithromycin on chemokine concentration in nasal mucosa in patients with acute uncomplicated bacterial sinusitis [26]. Both studies by Peric et al. used an unblinded design, which might have undermined the accuracy of the results. The sample size is sufficiently large in both studies to detect primary and secondary outcome changes. The later study by Peric et al. has another limitation: the control group did not receive any treatment.

Bromelain is a group of enzymes found in the fruit and stem of the pineapple plant. Passali et al. showed the presence of bromelain in the nasal epithelium and blood serum after oral administration [27]. A study by Buttner et al. concluded that oral administration of bromelain improved various clinical markers, such as Total Symptom score, Total Rhinoscopy score, and SNOT-20, mostly in patients suffering from CRS without nasal polyps [28]. Buttner et al. examined the effect of bromelain on twelve patients without a control, and the dosage used was not standardized. These limitations affect the results and conclusion and should be considered to hold a high risk of bias. Two studies examine the effect of bromelain in patients with ARS. The first study by Ryan et al. concluded that the addition of bromelain in the standard therapeutic regimen decreases mucosal inflammation and therefore improves the therapeutic result in patients suffering from ARS [29]; however, the results of their study (Table 2) do not clearly reflect their conclusion, as only mucosal inflammation was statistically improved, while the rest of the parameters remained unchanged or insignificantly changed. The second study, by Braun et al., examined the effect of monotherapy with bromelain in children (<11 years old) suffering from ARS [30]. Although the methodology of this study is well organized, treatment allocation was not blinded. Moreover, the dosage of the bromelain tablets and the frequency and dosage of the standard treatment were not mentioned. Moreover, the sample size, even though it could be considered sufficient, was unjustified by power analysis.

Nigella sativa is a plant endemic to the Mediterranean area. There is only one study by Rezaeian et al., comparing the nasal spray with *Nigella* with placebo for the treatment of CRSsP [31]. The sample size of this study is close to sufficient. The results and conclusions of this study may be affected by using sodium chloride 0.65% as a placebo-control. Hypotonic solution nasal rinses may lead to increased mucin production [32], which may negatively affect the patient's nasal congestion and rhinorrhea.

Manuka honey (MH) is a monofloral honey produced by bees that pollinate from the nectar of Manuka trees (*Leptospermum scoparium*), which are endemic in New Zealand and Australia. The active substance in the Manuka honey is methylglyoxal, and the content of this substance in the honey stratifies the honey in grades of strength. A study by Alandejani et al. shows that in vitro, Manuka honey acts against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms [33]. The in vivo study of Paramasivan et al. concluded that methylglyoxal-augmented Manuka honey has anti-biofilm properties in the nasal epithelium of animals that have been nasally irrigated with this substance [34]. Nasal irrigation with Manuka honey also affects the concentration of inflammatory markers, such as IL-6, IL-8, IL-13, MCP-1, and MIP-1β, in the nasal mucosa in patients who have undergone Functional Endoscopic Sinus Surgery, as Manji et al. showed

in their recent study [35]. Even though this study is well-designed and examines the effect of Manuka honey on a biochemical level, there is a major drawback. The levels of interleukins are different in each phenotype of CRS. The effect of Manuka honey on interleukins should be examined separately for each phenotype. Moreover, this study has a very small number of participants, and it is not safe to extrapolate accurate conclusions. Clinical studies on the effectiveness of Manuka honey showed often contradictory results. A single-blind study by Thamboo et al. in patients with Allergic Fungal Rhinosinusitis showed that there was symptomatic improvement (SNOT-22) but without concurrent endoscopic improvement [36]. A study by Lee et al. that examines cystic fibrosis patients who received postoperatively (FESS) nasal irrigations with Manuka honey showed non-statistically significant improvement of symptoms and statistically significant improvement in endoscopic findings, compared to natural saline irrigation [37]. Both studies (Thamboo et al. and Lee 2021 et al.) are single-blinded, and the second study includes an inadequate number of participants (n=10). Moreover, in the case of the Thamboo et al. study, the use of different treatments in each nostril may lead to uncontrolled results due to possible systematic effects of each drug. A study by Ooi et al. compares the effectiveness of Manuka honey and culture-driven antibiotic therapy in post-operative patients (FESS) and shows that the use of Manuka honey is safe but not superior to culture-directed antibiotics [38]. This study's small sample size is unjustified by power analysis, which might jeopardize the robustness of the evidence presented. A study by Lee et al. in 2017 did not show a statistical difference between Manuka honey irrigations and saline, but in a subset of patients that did not receive antibiotics or corticosteroids, culture negativity was statistically higher for Manuka honey [39]. Both Ooi et al. and Lee et al. have single-blinded designs. This lack of blinding may affect the self-reported SNOT 22 used in both studies. In the study by Lee et al., the only significant outcome (culture negativity) appeared in a subgroup of 10 patients, who did not receive either antibiotics or steroids, which, apart from the small sample size of the study, might predispose to selection bias. Moreover, the combination of small sample size and methodology (± antibiotics or steroids) might result in inadequate randomization and residual confounding.

ELOM 080 is a standardized herbal mixture containing oils from Eucalyptus, Lemon, (Sweet) Orange, and Myrtle in the ratio 66:32:1:1, and those plants give rise to its acronym. Preclinical studies showed that ELOM 080 has secretor-motor, mucolytic, and secretolytic actions affecting the mucociliary clearance of respiratory epithelium [40–42]. A multicentric double-blind randomized placebo-controlled study by Federspil et al. showed that ELOM 080 is significantly superior to placebo in the treatment of acute post-viral uncomplicated sinusitis [43]. This study by Federspil et al. provides a good quality of evidence with a low risk of bias due to its large sample size and well-designed methodology. Another study by Karpova et al. examined the use of ELOM 080 in the treatment of acute uncomplicated sinusitis in a pediatric population [44]. The study could not provide high-quality evidence due to its small sample size and unblinded methodology. Pfaar et al. showed that ELOM 080 is a safe and effective treatment for AVRS, as it reduced the severity of symptoms and alleviated the symptoms three days earlier than the placebo [45]. The clinical trial by Pfaar et al. is a very well-designed study possessing a low risk of bias. Wu et al. is the only study examining the effect of the standardized herbal mixture in children with CRSsNP [46]. A limitation is the possible small sample size, which undermines the sensitivity of the study. Furthermore, the diagnostic criteria used in this study are not clearly presented. Moreover, the control group receives antihistaminic medication, which is not recommended as part of the treatment of CRS. Finally, it should be noticed that there is a systematic review and meta-analysis in progress that examines ELOM 080 effects in both ARS and CRS [47].

BNO 1016 is an herbal mixture based on a dry extract of a fixed combination of five herbal drugs, including Gentian root (*Gentianae radix*), Primula flower (*Primula flos*), Sorrel herb (*Rumicis-herba*), Elder flower (*Sambuci flos*), and Verbena herb (*Verbenae herba*) in the ratio 1:3:3:3:3. Preclinical studies showed that the herbal mixture has antibacterial properties [48] and prophylactic antiviral properties [49], improves mucociliary clearance acting on various receptors such as CFTR and $Ca^{(2+)}$-dependent TMEM16A62 [50], and presents anti-inflammatory action by inhibition of production and expression of proinflammatory factors as PGE2 and COX-2, respectively [51]. BNO 1016 may provide statistically significant improvement in cases of acute viral rhinosinusitis when compared with placebo, as concluded by Jund et al. [52]. This study by Jund et al. is a well-designed study with a moderately low risk of bias, providing a valuable conclusion regarding the use of BNO 1016. The addition of BNO 1016 to the standard treatment for acute viral rhinosinusitis is safe and effective in children 2-5 years old, reducing the recovery time, providing faster relief of major symptoms, reducing mucostasis, and increasing the aeration of the middle ear [53]. This study by Sen'kevich et al. has a sufficient sample size and can be accounted as an accurate and valuable study from which it is possible to extrapolate safe conclusions. Passali et al. compared BNO 1016 with fluticasone spray, concluding that these drugs have the same therapeutic efficacy in the treatment of ARS [54]. According to the EPOS 2020 guidelines, fluticasone spray does not provide a positive effect on quality of life, and due to moderate quality of evidence, fluticasone is not the first line of treatment in ARS, making the comparison between BNO 1016 and fluticasone spray of little clinical importance. Moreover, this study has an unblinded methodology, which affects the self-reported SNOT 20.

Table 2. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Pimpinella anisum *SINUPIM*	CRS without Nasal Polyposis	Vazifehkah et al. (6) A single-blinded randomized trial.	n=48	A. Two Intranasal drops of P. anisum based herbal medicine BID, n=26 B. Two Intranasal fluticasone puffs (total dose of 200 μg) BID, n=22 Each nostril for 4 weeks	Statistically significant difference in reduction of SNOT – 22(P. anisum group 20.80 ± 16.24 vs Fluticasone group 10.36 ± 10.30, p =0.012) and mean reduction in Rhinological symptoms subscale of SNOT-22(need to blow nose, sneezing, postnasal discharge, runny nose) (P. anisum group 7.26 ± 4.38 vs fluticasone group 4.09 ± 3.22, (p=0.007) Non statistically significant difference in reduction of Lund-Mackay score (P. anisum group 2.22 ± 2.94 vs Fluticasone group 0.76 ± 1.39, p=0.067)	Sinupim group had significantly better outcomes than fluticasone spray group after 4 weeks of treatment.	Moderately low risk of bias Short treatment course
Matrricaria chamomilla	CRSsNP and mild CRSwNP	Nemati et al. (7) A randomized double-blind placebo-controlled trial.	n=74	A. Intranasal Ethanolic extract of M. Chamomilla, 3 drops TID, each nostril for 3 weeks, after saline irrigations, n=37 B. Sesame seed oil 3 drops TID, each nostril for 3 weeks after saline irrigations, n=37	Statistically significant improvement was presented in intervention group for: adjusted mean score of quality of life during 4 time periods (intervention group: 34.3 vs control group: 45.9, p=0.001) and endoscopy score (Grade I polyposis finding Interv. group: 21.6% vs control group: 48.6%, p=0.046 and inflammation/ discharge finding Interv. group 24% vs control group: 45.9%, p=0.03 Inter. group only	Chamomile extract achieves further reduction of the clinical symptoms and improvement of the quality of life than placebo in CRS patients.	Possible small sample size (No justification of sample size- no power analysis) Mixed CRS phenotypes Short treatment course. Moderately low risk of bias
Ecballium elaterium	"Sinusitis"	Sezik et al. (17)	n=49	Intranasal diluted juice-controlled dose	Improvement of both symptoms and imaging findings(X-ray) 71%, symptom relief only in 20%.	Further in vivo investigation is in progress	Poor methodology X-ray findings are not specific for ARS diagnosis and evaluation High risk of bias
Cyclamen europaeum (CE) Sinuforte®	ARS	Trestioreanu et al. (19) Metanalysis	2 studies- n=147	A. Lyophilized extract, 1.3 mg once daily in each nostril B. Placebo concomitant antibiotic use	Examining effectiveness and adverse events	Effectiveness could not be examined due to poor study design and small sample size. This evidence is moderately reliable according to the authors. No serious adverse effects. 50% of patients who received C. europeum reported minor adverse events compared with 24% in control group.	Well-designed study
Cyclamen europaeum (CE) *Sinuforte®*	ARS	Mullol et al. (20) Secondary pharmacoeconomic analysis Observational descriptive study	Pooled Data of 2610 patients with ARS	Intranasal use (dose is not clear)	Cure rate (according to EPOS- resolution of symptoms in 2-4 weeks) of monotherapy with C. europaeum is 15.3% higher than other monotherapies (P <.05) and 10.3 % higher when compared with other combination therapies (P <.05) . C. europaeum addition 2-drug combinations show statistically significant increased cure rate17.3%; P <.05 No significant cure rate increase was presented when C. europaeum is added to single drug or 3-drug combination	Cyclamen as monotherapy against ARS has better healing rates than other therapies without additional cost.	Observational descriptive study. Confounding factors may affect the results Moderately high risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Cyclamen europaeum (CE) *Sinuforte®*	ARS	Kriukov et al. (21) Randomized multicenter study.	n=120	A. Intranasal use of Sinuforte daily, n=60 B. Standard treatment, n=60	Data could not be retrieved.	Intranasal administration may be efficacious in the treatment of ARS.	Combined interventions were used in the control group that differed from the intervention group.
Cyclamen europaeum (CE) *Sinuforte®*	ARS	Ovchinnikov et al. (22) Randomized Controlled Trial	n=50	A. Intranasal use of Sinuforte (unidentified dose) + Amoxicillin/ Clavulanic acid BID + Xylometazole BID, n=25 B. Amoxicillin/ Clavulanic acid BID + Xylometazole BID, n=25	Data could not be retrieved.	Combination with antibiotics significantly improved dynamics of subjective and objective signs. Non-statistically significant improvement of mucociliary clearance.	Small Sample size Combined interventions were used in the control group that differed from the intervention group.
Cyclamen europaeum (CE) *Sinuforte®*	Acute exacerbations of CRSsNP (AECR)	Lopatin et al. (23) real-life, prospective, observational study	n=317 moderate total VAS:3-7 Acute exacerbation of CRS-sNP	A. Group 1 (n=124) C.europaeum -CE(2.6 mg once daily)+oral antibiotic for 8 days B. Group 2 (n=90) C.europaeum monotherapy C. Group 3 (n=99) Oral antibiotic only Empirical antibiotic therapy prescription followed the standards of national rhinosinusitis guidelines.	Total Nasal Symptom Score (TNSS): Starting from day 3 and at all following time points (day 5 , 8 and 6th week) CE + oral antibiotic and CE monotherapy showed statistically significant higher resolution of TNSS than oral antibiotic alone ($p<0.001$). Individual Nasal Symptom Score: Either oral antibiotic plus CE or CE in monotherapy induced a significantly ($p < 0.001$) higher resolution of nasal congestion and nasal discharge from day 5 to week 6 (T4) and from day 8 to week 6 compared to antibiotics in monotherapy. Hyposmia: No statistically significant change between treatment options. Nasal endoscopy assessment: Either oral antibiotic plus CE or CE in monotherapy, induced a significant ($p < 0.001$) reduction of the middle meatus mucosal oedema from day 3 to week 6. No significant change in Middle meatus discharge score between groups at 3-8 days however, on the 6th week the score in group 3 (oral antibiotic alone) was significantly ($p < 0.05$) higher than in group 2. Statistically significant less exacerbations for 6 month follow up for CE + antibiotic group ($p<0.01$)	CE extract nasal spray in monotherapy or added to standard antibiotic treatment significantly reduces sinonasal symptoms and CRS recurrences compared to antibiotic monotherapy. No severe adverse effects were recorded.	No randomization (high risk of selection bias) Not blinded study No justified sample size Moderately high risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Pelargonium sidoides (EPs 7630)	ARS presumed to be of bacterial origin.	Bachert et al. (24) A randomized, double-blind, placebo-controlled multicenter trial	n=103	A.EPs 7630-solution, ethanolic extract, 60 drops orally TID, n=51 B. placebo, n=52	Primary outcome: Mean decrease in Sinusitis Severity Score (SSS) at day 0 minus SSS at day 7 EP 7630:5,5 points, placebo: 2,5 showing statistically significant superiority of EP 7630 ($p<0.00001$). Statistically significant superiority ($p < 0.001$) of EP 7630 in all secondary clinical parameters: Headache, Maxillary pain Maxillary pain worsened when bending with percussion or pressure, Nasal obstruction Purulent nasal Secretion, Purulent postnasal discharge Investigator assessed treatment on day 7 $p < 0.0001$: Major improvement in 30% of patients receiving EPs 7630 vs 5.8% of placebo. Patient assessed treatment on day 7 |Major improvement: 34% EPs 7630 vs 3.8% of placebo	EPs 7630 was well tolerated and superior in efficacy than placebo.	Presumption of bacterial origin does not match the current definition of ABRS. Low risk of bias
Pelargonium sidoides (EPs 7630)	Uncomplicated ABRS – mild to moderate Total symptom score <8	Perić et al. (25) A Randomized, Open-Label study	n=50	A. EPs 7630 oral tablets 20mg TID for ten days n=25 B. Amoxicillin oral tablets 500mg TID for ten days n=25	Statistically significant higher absolute improvement of Total symptom score, nasal obstruction facial pain/pressure, impaired sense of smell, total endoscopic score, mucosal edema and mucopurulent secretions ($p<0.001$) in EP 7630 group. No significant improvement in rhinorrhea p=0,248 and postnasal drip p=0,679 EPs 7630 significantly decreased the rates of patients with positive bacterial cultures for S. pneumoniae($p<0.001$), H. influenzae($p=0.016$) and Moraxella catarrhalis ($p=0.031$), whereas amoxicillin treatment significantly reduces the percent of positive culture for S. pneumoniae ($p=0.002$ and H. influenzae ($p=0.031$) No adverse effects were reported.	Pelargonium has better clinical and antimicrobial efficacy than Amoxicillin oral tablets.	Unblinded Moderately low risk of bias
Pelargonium sidoides (EPs 7630)	Uncomplicated ABRS – mild to moderate Total symptom score <8	Perić et al. 2021 (26) A comparative prospective study	n=78	A. EPs 7630 oral tablets 20mg TID for ten days n=26. B. Roxithromycin oral tablets 150mg BD for ten days n=26. C. Control Group, no treatment, n= 26.	Statistically significant decrease of all clinical parameters (nasal obstruction, rhinorrhea, Postnasal drip, facial pain, loss of smell, total symptom score, Total endoscopic score, mucosal edema, mucopurulent discharge) in both EPs 7630 and roxithromycin ($p<0.001$). No improvement in control group Clinical effects were significantly better in roxithromycin group ($p<0.001$)except rhinorrhea($p=0.197$) and postnasal drip ($p=0.642$) with no statistically significant difference. Similar modulatory actions of the two drugs on monocyte and neutrophil functions in ABRS patients.	Both EPs 7630 and Roxithromycin treatment resulted in significant improvement in ABRS . Roxithromycin shows better clinical efficacy than EP7630.	Unblinded Control group did not receive placebo. Moderately low risk of bias
Bromelain	CRSsNP post sinus surgery	Buttner et al. (28) prospective, open-label observational pilot study	n=12	Bromelain tab 500 FIP Average daily dosage 3000 FIP for three months	Data could not be retrieved.	Improvement of Total Symptom score, Total Rhinoscopy score and SNOT-20, mostly in patients suffering from CRS without nasal polyps.	Observational design small sample size No control, no standardized dosage High Risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Bromelain	ARS	Ryan et al. (29) A Double-blind clinical evaluation	n=48	A. Group 1 :bromelain tablets (2 tabs BID for six days) n=23 B. Group 2: placebo n=25 Additionally, both groups received standard regimen with antibiotic (erythromycin PO or penicillin IM), antihistaminic decongestant & analgesics	Nasal mucosal inflammation recovery was statistically significant ($0.05 < p > 0.02$) in Bromelain group 83% vs 52% in placebo, the rest clinical parameters (nasal discharge, breathing difficulty, headache, facial pain) were unchanged or showed non statistically significant change. Good to excellent results: 87% of bromelain group vs 68% placebo group ($0.05 < p > 0.02$)	Addition of bromelain tb to standard regimen for ARS. Improves clinical efficacy of standard treatment.	Authors conclusions do not clearly reflect the study results. Modest sample size (power analysis was not provided) Moderately high risk of bias
Bromelain	Pediatric (<11 years old) ARS	Braun et al. (30) A Multicentric pharmacoepidemiologic cohort study	n=116	A. Monotherapy verum group: Bromelain-POS® 500 FIP units enzymatic activity per tablet (n=62), B. Combination therapy group: Standard therapies (e.g. decongestant + antibiotic usually amoxicillin, secretolytics) + Bromelain-POS® (n=34), C. Control group: standard therapies only (n=20)	Monotherapy verum group showed the statistically significant ($p=0.005$) shorter mean period of symptoms (6,66 days) compared with combination therapy group (7.95 days) and control group (9,06 days). A 10-year-old male showed a mild allergic reaction to Bromelain-POS® but treatment was continued.	Statistically significant faster recovery from symptoms in children with ARS receiving Bromelain monotherapy than Bromelain+ standard regimen (incl. Antibiotic) combination or standard regimen alone.	Bromelain doses were not mentioned. Sufficient sample size but a power analysis is absent. Moderately low risk of bias
Nigella sativa	CRSsNP mild to moderate	Rezaeian et al. (31) A randomized placebo controlled clinical trial	n=65	A. Intervention group: N. sativa nasal spray 2 puffs/ day (1 g/ day of N. sativa) for 8 weeks, n=31 B. Placebo group: sodium chloride spray 0.65%. 2 puffs/ day for 8 weeks n=34. Furthermore, all patients received Cetirizine 10mg/ day and Azithromycin 500mg/day.	After 8 weeks: Lund–McKay score (mean ± SD) Intervention group 2.93 ± 1.15, Placebo group: 4.81 ± 1.17 – $p<.0001$. Modified Lund-Kennedy (mean ± SD): Intervention group 1.54 ± 0.92, Placebo group 3.43 ± 1.16 – $p<.0001$. SNOT-22 score (mean ± SD): Intervention group 14.87 ± 5.01, Placebo group 23.15 ± 5.01 – $p<.0001$. No adverse effects.	Significantly lower Lund–McKay, Lund-Kennedy, and Sino-Nasal Outcome Test-22 scores in intervention group compared to placebo.	Sodium chloride 0,65% used in placebo group might be counter-effective in the treatment of CRS. Moderately low risk of bias.
Manuka honey/ Leptospirum Honey (LH)	CRS ± polyps – post FESS	Manji et al. (35) Placebo controlled clinical study.	n=41	A. LH group:5%–7% concentration solution in 240 ml power rinse® bottle nasal irrigator BID for 3 months following FESS, n=26 B. Placebo group: Distilled water reconstituted with pH-balanced sodium chloride and sodium bicarbonate mixture (Sinus Rinse™ sachet) BID for 3 months following FESS, n=15	Biopsies were taken during FESS, 5 weeks post-op and 12 weeks post-op . The Cytokines measured were significantly increased from baseline in patients receiving LH compared with placebo. IL-6 ($p=0.04$), IL-8 ($p=0.0398$), MCP-1 ($p=0.0284$) and MIP 1β ($p=0.016$)	LH might be beneficial in wound healing process in post FESS patients. LH treatment affects the production of certain cytokines that might affect variably the different CRS phenotypes.	Different CRS phenotypes were studied, even though their pathophysiology mechanisms are different. Moderately low risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Manuka honey/ Leptospirum Honey (LH)	AFRS - post FESS	Thamboo et al. (36) A randomized prospective single-blinded study	n=34, post FESS, received intranasal corticosteroids for 12 weeks and a trial of systemic antifungals and steroid without improvement	Standard medical management continued for both nostrils; however, one nostril was additionally sprayed with 2 mL of a 50/50 mixture of honey-saline solution once a day for 30 days.	The treatment group has a 1.74 units reduction in Endoscopic mucosal score compared to the control group (95% CI 25.02 to 1.55), but this was not statistically significant (p=0.2901). A significant improvement in SNOT-22 (p=0.022) was appreciated in patients who received honey- saline solution.	Manuka honey nasal sprays application resulted in symptomatic improvement (SNOT-22) but without concurrent endoscopic improvement.	Poor design due to treatment of each nostril separately. SNOT score cannot be calculated separately. Moderately high risk of bias due to the design of the study.
Manuka honey/ Leptospirum Honey (LH)	Recalcitrant Cystic Fibrosis CRS	Lee et al. (37) A prospective single-blinded, randomized, parallel, two arm pilot trial.	n=10 recalcitrant cystic fibrosis sinusitis post FESS	A. Manuka honey nasal irrigations BID (120ml each time) for 30 days – Formulation:24 ml of manuka honey paste mixed with 240 ml of water n=5, , n=5 B. 120 ml saline irrigation BID for 30 days n=5	Not statistically significant improvement in SNOT-22 score(p = .29) Statistically significant difference in reduction of Lund-Kennedy score in the MH group. MH (-3 [-5,-3]) versus saline (0 [0,0]) (P = .006) No difference in post-treatment culture negativity. No serious adverse events were present	No statistically significant change in quality of life Score. Statistically significant change in endoscopic score. Culture negativity was the same for saline and MH nasal irrigation.	Moderately low risk of bias
Manuka honey/ Leptospirum Honey (LH)	Recalcitrant CRS	Ooi et al. (38) phase 1 randomized, single-blinded, placebo-controlled trial	n=25, recalcitrant CRS post FESS	A. Control Group (CON) n=15: 240 ml isotonic saline irrigation + 10-day culture-directed antibiotic capsule course B. MH group (MH)n=10: 16.5% MH augmented with 1.3 mg/ mL in 240 ml nasal irrigation bottles + 20 placebo tablets Patients received irrigation BID for 14 days and a tablet BID for 10 days , patients were examined on 14th day	No statistically significant difference in UPSIT between groups: 2.8 (−1.6 to 7.2) p=0.2141 Adverse effects: no serious adverse events. No significant difference in post vs pre-Tx overall symptoms measured with VAS in both CON(p=0.0644), MH (p=0.7404) groups as well as no significant interaction between CON and MH group p=0.3427 No statistically significant reduction in SNOT-22 for both MH(p=0.314) and CON (p=0.079) group Statistically significant individual reduction of Lund-Kennedy score in both MH(p=0.015) and MH(p=0.0033) group, but no statistically significant difference between the two groups(p=0.7197)	MH with MGO is safe after application for 2 weeks but not superior to culture-directed antibiotic treatment.	Moderately low risk of bias. Insufficient duration of treatment

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
Manuka honey/ Leptospirum Honey (LH)	CRS and prior sinus surgery	Lee et al. (39) prospective single-blinded randomized controlled trial	n=42	A. Manuka Honey irrigation group n=20 (MH) B. Saline irrigation group n=22 (SAL) BID for 30 days and oral antibiotics, oral/topical steroids as indicated	Statistically significant improvements for both groups in SNOT -22 but no statistically significant difference between the two groups MH: -12 and SAL: -12,5(p = 0.57) No statistically significant difference in Culture negativity between the groups MH (8/19, 42%) vs SAL (4/21, 19%), (p=0.11). No statistically significant difference between the groups in Lund-Kennedy score MH: -3 vs SAL: -1 (p = 0.20) For a subgroup of patients not receiving oral antibiotics/ steroids MH (5/10, 50%) compared to SAL (0/6, 0%). No adverse events.	No statistically significant difference between the two groups. Culture negativity was statistically significant for a subgroup of patients who did not receive oral antibiotics/steroids.	Moderately low risk of bias. Sufficient sample size for primary outcome (SNOT-22)
ELOM 080/ Myrtol/ GeloMyrtol® forte/ Myrtol® Standardized	ARS Acute Post-viral Rhinosinusitis	Federspil et al. (43) A double-blind, randomized placebo-controlled multicenter study	n=330	A. Myrtol group: GeloMyrtol® forte 300mg/ capsule QID (4 times a day) for 6±2 days, n=109 B. Essential oil (unregistered) Group: Essential oil 300mg QID for 6±2 days, n=110 C. Placebo group: capsules QID for 6±2 days, n=111. Each group received two puffs in each nostril daily for 4 days	Statistically significant Symptom score reduction in Myrtol and essential oil group (p=0.02) Need for Antibiotics - Myrtol group 23% Essential oil group 37% Placebo Group 40%	ELOM 080 and other essential oil are significantly superior to placebo in the treatment of acute post-viral sinusitis. Tolerance was slightly better for Myrtol standardized group.	Well-designed study Sufficient sample size Low risk of bias
ELOM 080/ Myrtol/ GeloMyrtol® forte/ Myrtol® Standardized	Pediatric uncomplicated ARS	Karpova et al.(44) A randomized parallel-group comparative study	n=60 6 to 10 years	A. Myrtol group: Myrtol 120mg TID for 7 days, n=30 B. Control group: conventional therapy only for 7 days Both groups received conventional therapy: an antibiotic + decongestant + nasal irrigation solution for 7 days	VAS for rhinorrhea, coughing and congestions showed significant (p<0.05) lower values in the Myrtol Group. Use of vasoconstrictive agents for Myrtol standardized was 2.2±0.4 days in comparison with 3.6±0.5 days in the control group.	Myrtol® Standardized is a safe, effective, and convenient method for the treatment of pediatric uncomplicated ARS.	Moderately high risk of bias
ELOM 080/ Myrtol/ GeloMyrtol® forte/ Myrtol® Standardized	AVRS	Pfaar et al. (45) A Randomized, Placebo-Controlled, Blinded Clinical Trial	n=447	A. ELOM-080 (GeloMyrtol® forte; containing 300 mg distillate of a mixture of four rectified essential oils) capsules 4 times a day for two weeks, n=225 B. matching placebo capsules 4 times a day for two weeks, n=222	Major symptom score assessed by the investigator: ELOM-080 was statistically significantly superior compared to placebo at day 7 +/-1 (p = 0.016) and day 14 +/-1 (p = 0.014). At the end of the treatment the number of patients considered to be cured MSSinv≤1 was significantly higher in ELOM 080 group than placebo group (p=0.006) Major symptom score assessed by the patient: decreased to 1.17 ± 0.2 (ELOM-080) and to 2.05 ± 0.2 (placebo) at visit 4 (p = 0.0029). No changes in olfaction tests, Significant absolute SNOT-20 score reduction for ELOM 080 on the second week post treatment: 6.0 ± 0.8 (ELOM-80) versus 8.0 ± 0.8 (placebo) (p = 0.07). No serious adverse events were reported	ELOM is safe and effective for the treatment of AVRS. Remissions of symptoms occurred three days earlier in ELOM 080 group compared to placebo	Well-designed study Low risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
ELOM 080/ Myrtol/ GeloMyrtol® forte/ Myrtol® Standardized	CRSsNP	Wu et al. (46) A prospective comparative observational study	n=69 children aged 4- 10 years old	A. Myrtol® Standardized, 3 capsules of 300mg daily + ephedrine 1 % nasal drops for 3 months, n=41 B. Chlorpheniramine oral tablets, 4 tablets pf 4 mg + ephedrine 1% nasal drops for 3 months, n=28	No statistically significant difference in remission time: Gelomyrtol forte:5,7+/-3.7 days Chlorpheniramine: 6.9 +/- 3.4 days p>0.05 Statistically significant total effective rates for Gelomyrtol, p<0.01 Significantly lower adverse reaction rates in the treatment group, p<0.05	Gelomyrtol is more effective than antihistamine in the treatment of pediatric CRS	Possible small sample size (no power analysis is specified) Antihistamine is not considered sufficient treatment for CRS Absence of standardized diagnostic criteria for chronic sinusitis Moderately high risk of bias
BNO 1016 – Sinupret®	Viral ARS	Jund et al. 01/2015 (52) A prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (pooled analysis)	n=600	A. BNO 1016 160 mg, TID for 15 days, n=303 B. Placebo orally TID for 15 days, n=297	Major symptom score at day 14 improved gradually in both groups, the difference between treatment groups was statistically significant in favor of BNO 1016, p<0.0001 Each individual symptom showed significant improvement in BNO 1016 group (p<0.0001) SNOT 20 at day 14 was statistically lower in BNO 1016 group than placebo group, p=0.0015 A four-day faster recovery was seen with BNO 1016. Complete recovery of symptoms and signs, normal rhinoscopy	Daily intake of 480 mg of BNO 1016 for 15 days is an effective treatment in acute viral rhinosinusitis.	Well-designed study Low risk of bias
BNO 1016 – Sinupret®	paediatric Acute Viral Rhinosinusitis	Sen'kevich et al. (53) an open, randomized prospective comparative clinical study.	n=82 4 – 5 years old	A. Group 1: BNO 1016 age adjusted dose + nasal rinses and topical decongestants n =30 B. Group 2: nasal rinses with isotonic solution + topical decongestants + Fluimucil antibiotic IT 125 mg 1-2 times a day through a compressor inhaler n=22 C. Group 3: nasal rinses and topical decongestant Placebo n=30	Complete recovery of symptoms and signs, normal rhinoscopy Group 1: 7th day Group 2: 10th day Group 3: 14th day	Safe and effective in children 2-5 years old. Sinupret improves the effectiveness of therapy and shortens treatment time.	Sufficient sample size to detect significant differences Moderately low risk of bias
BNO 1016 – Sinupret®	ARS	Passali et al. (54) A prospective open-label study,	n=60	A. Group 1: Sinupret® Forte, 1 tablet TID for 14 days n=30 B. Group 2: Fluticasone, spray 2 puffs in each nostril daily for 14 days n=30	All patients showed statistically significant improvement in Mean symptom score measured by investigator on the 14th day, Group 1: 1.8 (day 0: 12.3) Group 2: 1.5 (day 0: 10.9). No statistically significant difference between groups, p=0.7589 SNOT 20 at the 14th day, Group 1: 7 (day 3: 28.5) Group 2: 6.5 (day 3: 25). No statistically significant difference between groups, p=0.712. No serious adverse events.	Same therapeutic efficacy as fluticasone spray.	Fluticasone spray is not currently the drug of choice in the treatment of ARS. Day 0 SNOT 20 was measured but not presented in this study Unblinded study design. Moderately high risk of bias

Table 2 *continued*. Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
BNO 1016 – Sinupret®	ABRS	Neubauer et al. (55) Placebo-controlled, randomized double-blind clinical trial.	n=160	A. Group 1: Sinupret®, 2 tablets TID for 14 days, n=81 B. Group 2: placebo 2 tablets TID for 14 days n=79 Both groups received Xylometazoline spray + Doxycycline tabs	After 2 weeks of therapy Group 1/Group 2 showed respectively 60.3%/25% no remaining symptoms, while 35.5%/50% of patients reported good effect, and 4.2%/25% reported no effect, p=0.00 Radiographic improvements showed a significant difference in favor of the Sinupret® group compared to the placebo, with a χ^2= 15.5049 and a p= 0.0084 Facial pain relief after 2 weeks mean score: Statistically significant lower mean score(p=0.0147) in ELOM-080 group. ELOM 080 pain relief was 1.2 days earlier than BNO 1016 Other symptoms as headache (differences in baseline versus end of treatment, ELOM 080: -5,1 vs BNO 1016: -4,4), nasal congestion (ELOM 080: - 5,3 vs BNO 1016: -4,9) trigeminal pressure point pain (ELOM 080: - 4 vs BNO 1016:-4,1) and sinus percussion pain (ELOM 080: -4,4 vs BNO 1016:-4,4) were relieved equally or showed non statistically significant difference. Patient satisfaction regarding the feeling of general illness: ELOM-080: 15.8, BNO 1016: 105.9 Statistically significant difference p<0.05. For the general assessment of relief of symptoms, the mean values were higher for ELOM, although the difference was not statistically significant. No statistically significant difference in physician's Global assessment of effectiveness and tolerability, p=0.4271	ELOM-080 and BNO 1016 showed similar efficacy, although the treatment with ELOM-080 resulted in a more rapid and more complete recovery in ARS.	Non-interventional parallel study Moderately low risk of bias
BNO 1016 – Sinupret®	CRSsNP	Palm et al. (59) A randomized double-blind placebo-controlled trial.	n=929	A. Sinupret 240mg group, Sinupret 80mg/tab, 1 tablet TID for 12 weeks, n=318 B. Sinupret 480mg group Sinupret 80 mg, 2 tablets TID for 12 weeks, n=305 C. Placebo group, n=306	Primary endpoint: Average Mean symptom score assessed by investigator in 8th week and 12th week Sinupret 240mg: 5.1 (baseline 10.7) Sinupret 480mg: 5.1 (baseline 10.7) Placebo: 5.3 (baseline 10.8) No statistically significant difference between the groups p>0.05 No serious adverse effects. Drug-related mild to moderate adverse effects: BNO 1016 240mg:4.4% BNO 1016 480mg: 5.9%, placebo:3.9 % Post hoc analysis showed that subgroup of patients diagnosed by ENT specialist, MSS >9 and duration of symptoms > 1 year showed significant results when treated with Sinupret® 480mg (MSSinv 8-12th week:5.3) vs placebo(MSSinv8-12th week:6.8) p=0.001	Sinupret is safe in patients with CRS. A subgroup of patients diagnosed by a specialist revealed significant therapeutic results. Sinupret extract was not superior over placebo regarding the primary endpoint.	Low risk of bias Post hoc analysis

Table 2 *continued.* Literature review of herbal products use in rhinosinusitis and critical evaluation.

Herbal medication	Disease	Type of study	Population	Formulation	Results Main Clinical Outcomes examined are highlighted	Conclusions	Critical evaluation
BNO 1016 – Sinupret®	Anosmia in CRS	Reden et al. (57) A Double-blind placebo- controlled study	n=36 Patients with sinonasal disease received prednisone for 7 days.	Prednisone for 7 days followed by either A. Sinupret® dose was not specified , TID for two months B. Placebo TID for two months	Good Safety and tolerability results Significant improvement of TDI in both groups ($p<0.05$) but with no significant difference in TDI (olfactory) score between Sinupret® and placebo ($F [df = 2] = 0.28$; $p = 0.67$)	No major differences in olfactory function between placebo and BNO 1016 groups.	Moderately high risk of bias.
BNO 1016 – Sinupret®	ARS	Bittner, et al. (58) Metanalysis of the clinical trials ARhiSi-1 (EudraCT No. 2008-002794-13) and ARhiSi-2 (EudraCT No. 2009-016682-28) and Retrospective cohort study	n=676 n=203.382	A. BNO 1016 480mg daily B. Placebo	BNO1016 treatment resulted in statistically significant reduction of Major symptom score (MSS) and SNOT 20. Least squares (LS) mean difference of MSS at day 14 between BNO 1016 group and placebo group was 1.9 ($p < 0.0001$) LS mean difference of SNOT 20 was 3.5 between BNO 1016 and placebo($p = 0.001$) In patients with moderate to severe symptoms, BNO 1016 even more pronounced results MSS: -2.3 points ($p < 0.0001$); SNOT-20: -4.9 points ($p = 0.0158$) BNO 1016 was as effective or significantly more effective in reducing the risk for adverse ARS-related events compared to antibiotics.	BNO 1016 is a safe and effective treatment for ARS which may reduce the use of antibiotics.	Well-designed study Real-life effectiveness of BNO 1016 Possible confounding factors due to study design
Xiangju	"Sinusitis" Presumed to be CRS	Xi et al. (60) A systematic review and Metanalysis	n=4331	A. Experimental Group 1. Conventional treatment + Xiangju capsules or 2. Conventional treatment + Eucalyptol-limonene-pinene Enteric soft capsules + Xiangju or 3. Conventional treatment + clarithromycin + Xiangju, n=2196 B. Control Group 1. Conventional treatment only) or 2. Conventional treatment + Eucalyptol-limonene-pinene Enteric soft capsules or 3. Conventional treatment + clarithromycin, n=2135 Xiangju dose was 0.9-2.7 g Treatment period varies between studies from 15 to 90 days.	1. Xiangju + Conventional treatment showed more significant efficiency ($p<0.00001$), total response rate($p<0.00$ 001), and Lund-Mackay scores($p<0.00001$) than conventional therapy alone. 2. Xiangju + Eucalyptol-limonene-pinene Enteric soft capsules + Conventional treatment showed significantly better total response rate ($p<0.0001$) and VAS scores for headache, congestion, olfactory function, facial disorder ($p<0.00001$) than Eucalyptol-limonene-pinene Enteric soft capsules + Conventional treatment 3. Xiangju + clarithromycin + Conventional treatment significantly better total response rate ($p<0.00001$), no significant difference was observed in efficiency ($p=0.07$) compared with clarithromycin + Conventional treatment	The addition of the herbal capsules resulted in increased symptomatic relief (VAS score), clinical improvement (Lund MacKay) and imaging improvement (CT scan score) when compared to standard treatment against CRS, without any adverse effects.	Well-designed study Phenotypes of CRS were not clear

Table 3. Evaluation of the risk of bias in RCTs and cohorts according to the Table 2 criteria.

Study	Study Design	Random sequence generation	Allocation concealment	Intent-to-treat analysis	Double-Blind or independent assessment	Co-interventions applied equally	Follow up rate >80%	Adequate sample size	Risk of Bias
Vazifehkah et al. [6]	RCT	+	+	-	Single (clinician)	+	+	+	Moderately low risk
Nemati et al. [7]	RCT	+	+	-	+	+	+	Not clear	Moderately low risk
Sezik et al. [17]	Cohort	-	-	-	-	Not clear	NM	-	High risk
Mullol et al. [20]	Cohort	NA	NA	NA	-	-	Not clear	+	Moderately high risk of bias
Kriukov et al. [21]	RCT	+	UD	UD	UD	-	UD	+	Cannot be determined
Ovchinnikov et al. [22]	RCT	-	UD	UD	UD	-	UD	-	Cannot be determined
Lopatin et al. [23]	Cohort	NA	NA	NA	-	-	+	+	Moderately high risk
Bachert et al. [24]	RCT	+	+	+	+	+	+	+	Low risk
Perić et al. 2020 [25]	RCT	+	+	-	-	+	+	+	Moderately low risk
Perić et al. 2021 [26]	RCT	+	-	-	-	+	+	+	Moderately low risk
Buttner et al. [28]	Observational study	NA	NA	NA	UD	Not clear	+	-	High Risk
Ryan et al. [29]	RCT	NM	NM	-	+	-	+	Not clear	Moderately high risk1
Braun et al. [30]	Cohort	NA	NA	NA	+	+	+	+	Moderately low risk
Rezaeian et al. [31]	RCT	+	+	-	+	+	+	+	Moderately low risk
Manji et al. [35]	RCT	+	NM	-	-	+	+	-	Moderately low risk
Thamboo et al. [36]	RCT	+	+	-	Single (clinician)	+	+	+	Moderately high risk2
Lee et al., 2021 [37]	RCT	+	+	-	Single (clinician)	-	+	-	Moderately low risk
Ooi et al. [38]	RCT	+	+	-	Single (clinician)	+	+	-	Moderately low risk
Lee et al., 2017 [39]	RCT	+	+	-	Single (clinician)	+	+	+	Moderately low risk
Federspil et al. [43]	RCT	+	+	+	+	+	+	+	Low risk
Karpova et al. [44]	Cohort	NA	NA	NA	-	+	+	-	Moderately high risk
Pfaar et al. [45]	RCT	+	+	+	+	+	+	+	Low risk
Wu et al. [46]	Cohort	NA	NA	NA	NM	+	+	Not clear	Moderately high risk
Jund et al. [52]	RCT	+	+	-	+	+	+	+	Moderately low risk
Sen'kevich et al. [53]	RCT	+	+	-	+	+	+	+	Moderately low risk
Passali et al. [54]	Cohort	NA	NA	NA	-	Not Clear	+	+	Moderately high risk
Neubauer et al. [55]	RCT	+	+	-	+	+	+	+	Moderately low risk

Study	Study Design	Random sequence generation	Allocation concealment	Intent-to-treat analysis	Double-Blind or independent assessment	Co-interventions applied equally	Follow up rate >80%	Adequate sample size	Risk of Bias
Gottschlich et al. [56]	Cohort	NA	NA	NA	+	+	+	+	Moderately low risk
Reden et al. [57]	RCT	NM	NM	-	+	Not clear	-	-	Moderately high risk[1]
Bittner et al. [58]	Cohort	NA	NA	NA	+	-	+	+	Moderately low risk
Palm et al. [59]	RCT	+	+	+	+	+	+	+	Low risk

NA: not applicable, UD: unretrieved data, NM: not mentioned. 1. According to Criteria presented in Table 2, Reden et al. and Ryan et al. RCTs should be evaluated as moderately low risk of bias, but due to the absence of important information in the article regarding the randomization and allocation to treatment as well as the power analysis, we decided to downgrade to moderately high risk. 2. According to Criteria presented in Table 2, Thamboo et al.'s RCT should be evaluated as moderately low risk of bias, but we decided to downgrade it due to the design of the study, as each patient sprayed one nostril only and evaluated with SNOT-22 each nostril separately which is not methodologically accurate as systematic effects might affect the results.

It should also be noted that day 1 SNOT was measured but was not mentioned in the study. A study by Neurbauer et al. concluded that the addition of BNO 1016 to standard ABRS treatment provides faster and better symptomatic relief [55]. The major drawback of this study is the utilization of radiological findings (X-ray) to diagnose and compare the efficacy of the different drugs, which may not present an accurate picture. A study by Gottschlich et al. compared the previously mentioned ELOM 080 with BNO 1016 against ARS, concluding that even though both herbal mixtures are effective in the treatment of ARS, ELOM 080 resulted in faster and more total therapeutic results [56]. This is in general a well-designed cohort, which compares the efficacy of two herbal drugs. A study on patients with anosmia due to CRS shows that the addition of BNO 1016 to prednisolone treatment does not provide increased therapeutic outcome [57]. This study includes a small number of participants. Bittner et al.'s meta-analysis concluded that BNO 1016 is safe and effective in the treatment of ARS [58]. Their research presents a large sample size and accurate methodology, resulting in a high quality of evidence with a moderately low risk of bias. BNO 1016 has been studied for its effect against CRS in a large study (929 patients) by Palm et al. The initial results on the 8th week demonstrated the safety of BNO 1016 use against CRS but failed to show significant improvement in symptoms. Then, those patients that suffered from severe CRS were selected by specialists. This group of patients achieved better therapeutic results than those with mild CRS after receiving BNO 1016 [59]. This study suffers from selection bias as the diagnosis was made by specialists along with general practitioners. Using this inclusion criteria, there were no significant different results between drug and placebo. Only in the post hoc analysis was it clear that an effect exists.

Xiangju is an herbal mixture of Platycarya Strobilacea Sieb, Astragali Membranacei Radix, Angelicae Dahuricae Radix, Spica Prunellae, Magnoliae Officinalis Flos, Glycyrrhiza Radix et Rhizoma, and Chrysanthemi Inidci Flos that is administrated per os as a capsule. The efficacy of this herbal mixture against CRS has been studied thoroughly. The systematic review and meta-analysis of Xi et al. supported the addition of Xiangju in the standard treatment of CRS [60]. This systematic review and meta-analysis provide high-quality evidence on the addition of Xiangju to the routine treatment in CRS.

Discussion

This study aims to review and evaluate the current literature on herbal preparations used for the treatment of ARS and CRS. An important limitation of the studies included in this review is that only a fraction of the studies evaluated examine the efficacy of an herbal product in specific ARS or CRS phenotypes. ARS phenotypes such as acute bacterial, viral, or post-viral rhinosinusitis might share some common characteristics but follow different pathophysiologic mechanisms and present a variable complication rate and severity. Therefore, herbal products should be examined specifically for each ARS phenotype. The guidelines should specifically state the phenotype of ARS against which the recommended herbal product has been tested and its efficacy has been approved. The same discussion applies to CRS phenotype classification, whereas the pathophysiologic mechanism is different. CRSwNP is mostly a type 2 inflammation mediated by Th2 lymphocytes through IL-4, IL-5, and IL-13, while CRSsNP could be either type 2 or non-type 2 inflammation mediated by TH1 via IFNγ and TNFα and TH17 via IL-17, IL-22, and IL-23 [5], and therefore different substances might affect each phenotype differently.

Table 4. Evaluation of the sum of the literature for each herbal product.

Herbal formulation	Disease	Summary of evidence	Comments	Quality of evidence
Pimpinella anisum-SINUPIM	CRSsNP	One RCT with a moderately low risk of bias	Supports the use of *P. anisum* compared with fluticasone spray	Moderate quality
Matrricaria chamomilla	CRSsNP and mild CRSwNP	One RCT with a moderately low risk of bias	Supports the use of *M. chamomilla* drops intranasally	Moderate quality
Ecballium elaterium	ARS	One unclear cohort with a high risk of bias	Unclear methodology, unretrieved data	Low quality
Cyclamen europaeum, Sinuforte®	ARS	One Metanalysis, two RCTs with an unclear risk of bias, one Cohort with a moderately high risk of bias	Metanalysis shows that *Cyclamen europaeum* is safe. Effectivity could not be evaluated due to the low quality of included RCTs.	Low quality
	AECR	One Cohort with a moderately high risk of bias	Supports monotherapy or the addition of *C. europeum* to antibiotic therapy	Low quality
Pelargonium sidoides (EPs 7630)	ABRS uncomplicated	One RCT with a low risk of bias Two RCTs with a moderately low risk of bias	Supports the use of P.sidoides	Moderate quality
Bromelain	ARS	One RCT with a moderately high risk of bias	Addition of bromelain to the standard regimen	Low quality
	Pediatric ARS	One Cohort with a moderately low risk of bias	Monotherapy with Bromelain shows faster recovery from ARS symptoms	Moderate quality
	CRSsNP Post sinus surgery	One Observational study with a high risk of bias	Supports the use of Bromelain tablets	Low quality
Nigella sativa	CRSsNP	One RCT with a moderately low risk of bias	Supports the use of *N. sativa* spray	Moderate quality
Manuka honey/ Leptospirum Honey	AFRS Post sinus surgery	One RCT with a moderately high risk of bias	Symptomatic improvement (SNOT 22)	Low quality
	Recalcitrant Cystic fibrosis CRS Post-sinus surgery	One RCT with a moderately low risk of bias	No statistically significant change in quality of life and culture negativity	Moderate quality
	CRS Post sinus surgery	Three RCTs with a moderately low risk of bias	Incongruent results	Low quality
ELOM 080 – Myrtol/ GeloMyrtol® forte/ Myrtol® Standardized	Acute (Post Viral) rhinosinusitis	One RCT with a low risk of bias	Supports the use of ELOM 080	Moderate quality
	Acute Viral Rhinosinusitis	One RCT with a low risk of bias	Supports the use of ELOM 080	Moderate quality
	Pediatric ARS	One Cohort with a moderately high risk of bias	Supports the use of ELOM 080	Low quality
	Pediatric CRSsNP	One Cohort with a moderately high risk of bias	Supports the use of ELOM 080 compared with antihistaminic drugs	Low quality
BNO 1016 – Sinupret®	Acute Viral Rhinosinusitis	One RCT with a moderately low risk of bias	Supports the use of BNO 1016	Moderate quality
	ARS	One Metanalysis and Cohort with a moderately low risk of bias	Supports the use of BNO 1016	High quality
	pediatric Acute Viral Rhinosinusitis	One Cohort with a moderately high risk	Supports the use of BNO 1016	Moderate quality
	CRSsNP	One RCT with a low risk of bias	Post-hoc analysis only showed a significant positive effect	Moderate quality
	Anosmia in CRS	One RCT with a moderately high risk of bias	No difference in olfaction between BNO 1016 and placebo	Low quality
BNO-1016 vs ELOM-080	ARS	One Cohort with a moderately low risk	Supports the use of ELOM 080	Moderate quality
Xiangju	CRS	One Systematic review and metanalysis	Addition of Xiangju to the standard treatment improves the oucome	High quality

Only one formulation is contraindicated due to serious adverse effects related to its use. *Ecballium elaterium* has been widely evaluated in literature. Due to a great number of case reports, which highlight its serious adverse effects of upper airway edema overshadowing the possible positive effects that have been presented in a few low-quality clinical trials, *E. elaterium* should be avoided under any circumstance until high-quality evidence supports otherwise.

Acute Rhino Sinusitis (ARS)

BNO 1016 is an herbal formulation supported for its efficacy against ARS by high-quality evidence in the literature. ELOM 080 is supported by moderate quality of evidence in cases of acute viral and post-viral sinusitis, as well as *P. sidoides* for acute bacterial rhinosinusitis. A non-interventional study by Gottschlich et al. [54] compares the efficacy of ELOM 080 with BNO 1016, concluding both showed similar efficacy, but ELOM 080 resulted in more rapid and complete recovery in ARS. Bromelain presents low quality of evidence in ARS cases. *Cyclamen europaeum* use against ARS has been thoroughly evaluated by numerous studies that support its use. However, a meta-analysis by Trestioreanu et al. advocates the safety of *C. europaeum* in patients with ARS, but its efficacy could not be evaluated due to the poor design of the existing RCTs [24]. Therefore, we consider that *C. europaeum*'s efficacy against ARS is supported by low-quality evidence. This contradicts the 1b level of confidence, which is presented in EPOS 2020 [5]. EPOS 2020 includes the same two studies (Ponikau et al. [71] and Pfaar et al. [72]) that have been evaluated in the aforementioned meta-analysis. Trestioreanu et al. downgrade the quality of these studies specifically due to small size, with high dropout in the Ponikau 2012 study, as well as both studies lack of reporting of concealment of allocation to treatment and lack of blinding on the evaluators side.

Pediatric Acute RhinoSinusitis (pARS)

BNO 1016 addition to the standard regimen. Braun et al. concluded that the use of bromelain-only therapy in uncomplicated pARS resulted in statistically significant faster recovery than the combination of bromelain and standard regimen [37]. This study has a moderately low risk of bias, and consequently it could be considered as a moderate quality of evidence. ELOM 080 efficacy in pARS is supported by low quality of evidence.

Chronic RhinoSinusitis (CRS)

Xiangju is the only herbal mixture that is supported by high-quality evidence in the treatment of CRS. Xi et al.'s systematic review and large meta-analysis support the addition of Xiangju herbal mixture capsules in the standard regimen in patients with CRS [60]. *P. anisum* and *Nigella sativa* present moderate quality of evidence specifically for patients with CRSsNP, as well as *M. chamomilla* for patients suffering from CRSsNP and mild CRSwNP. Bromelain and Manuka honey use for the treatment of CRS (and AFRS in the case of Manuka honey) present low quality of evidence in the existing literature. Bromelain, as well as Manuka honey, have been extensively studied, but the results of the different studies were often contradictory in the case of Manuka honey or extrapolated from poor methodology and small-sized trials in the case of bromelain. In the case of BNO 1016, its use in CRS cannot be supported. The only existing study is that of Palm et al. [69], whose primary analysis did not present any significant change in the symptom score. A post hoc analysis revealed a significant change, which should not be regarded as definitive proof.

Conclusion

Only BNO 1016 efficacy against ARS is supported by high-quality evidence. The same applies for the addition of Xiangju capsules in the standard regimen against CRS. Regarding the remaining herbal preparations, a few promising herbal drugs might exist but need to be further evaluated by high-quality clinical trials and meta-analyses before they could be safely and accurately recommended for the treatment of ARS and CRS.

Authors' contributions

KC: Acquisition, analysis, interpretation, and revision of the data, authoring; EP: Conception of the topic and supervision; AK: Research guidance, revision of the article, supervision; CS: Supervision; IV: Supervision.

Funding

This project did not receive any funding.

Conflicts of interest

No conflict of interest.

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Rhinology 63: 3, 0 - 0, 2025
https://doi.org/10.4193/Rhin23.526

Received for publication:
December 29, 2023
Accepted: March 8, 2025

Assocociate Editor:
Basile Landis