INTRODUCTION

Acute rhinosinusitis (ARS) is one of the most common infections of the upper respiratory tract and affects a significant proportion of the population. In the US alone, people with sinus disorders spend more than $2 billion annually, and make 1 million physician visits each year in pursuit of symptomatic relief. For adults seeking care in ambulatory medical practices, sinusitis is the most common diagnosis and is treated with antibiotics. The clinical diagnosis of acute rhinosinusitis (ARS) in children is challenging, due to the overlapping of symptoms with other ordinary childhood nasal diseases, such as viral upper respiratory tract infections and allergic rhinitis, not to mention the difficulties related to physical assessment. ARS in children is defined as the sudden onset of two or more of the following symptoms, lasting less than 12 weeks: discoloured nasal discharge, nasal blockage/congestion, cough in the day and nighttime. Rhinosinusitis is an inflammatory process involving
the mucosa of the nose and sinuses. It is a multifactorial disease, in which factors such as mucociliary impairment, infection, allergy and swelling of the nasal mucosa can contribute to its genesis, maintenance and recurrence. Antibiotics are the most frequently used therapeutic agents in ARS, while there is reasonable evidence to support the addition of intranasal steroids.

Phytotherapy is the use of extracts of natural origin as medicines or health-promoting agents. Phytotherapeutic medicines differ from plant-derived medicines in their standard pharmacology. Whereas standard pharmacology isolates an active compound from a given plant, phytotherapy aims to preserve the complexity of substances from a given plant, with relatively less processing. In herbal medicine, plant material that has been processed in a repeatable operation, so that a discrete marker constituent is at a verified concentration, is then considered standardised. The quality of crude drugs or plant medicines depends upon a variety of factors, including the variability in the species of plant being used, the plant’s growing conditions, timing of harvest, post-harvest processing and storage conditions. Modern phytotherapy may use traditional methods of assessment of herbal drug quality, but more typically relies on modern processes, such as HPLC (high performance liquid chromatography), GC (gas chromatography), UV/VIS (ultraviolet-visible spectrophotometry) or AA (atomic absorption spectroscopy). Complementary/alternative medicines are extensively used in the treatment of both ARS and chronic RS, but evidence-based recommendations are difficult to propose due to the lack of randomised controlled trials and methodological problems in many clinical studies and trials. To date, there are only a few double-blind, placebo-controlled, randomised studies that have assessed the efficacy of herbal compounds in treatment of ARS, which is not representative of the full spectrum of herbal remedies used in the treatment of ARS. Different herbal drugs have been proposed for the treatment of ARS.

Cyclamen europaeum extract (Nasodren®) is rich in saponins, which acts as a local surfactant on the mucous membranes to promote the intranasal drainage of fluid from the sinuses through a physical mechanism. Cyclamen is a member of the primrose family (Primulaceae) and has been used medicinally since ancient times. For example, Theophrastus in ancient Greece (4th–3rd centuries BC) recommended inserting a mixture of cyclamen extract and honey into the nose to treat nasal catarrh and headaches (“to clear the head”). Cineole is a terpenoid oxide present in eucalyptus oils, amongst others. Eucalyptus has been shown to have anti-inflammatory, antiseptic and decongestant properties, and is traditionally used to treat asthma, nasal congestion, runny nose, cough, sore throat and sinusitis.

Bromelain is a proteolytic enzyme obtained from pineapple. Its physiological effects appear to include interactions with inflammatory, immune, cell signalling, coagulation molecules and related pathways. The enzyme’s anti-inflammatory action is due to its inhibition of bradykinin production at the inflammatory site.

Andrographis paniculata is an annual herbaceous plant of the family Acanthaceae, native of India and Sri Lanka. The herb has a number of purported medicinal uses, although research has found that evidence of its effectiveness is limited to the treatment of upper respiratory tract infections, ulcerative colitis and rheumatic symptoms. Kan Jang® contains Andrographis paniculata and Eleutherococcus senticosus and may shorten the duration and lessen the symptoms of common cold.

Angocin® Anti-Infekt N contains mustard oils (isothiocyanates) that inhibit the growth of bacteria and viruses. It also contains natural antibiotics from nasturtium and horseradish, which make it effective in the treatment of respiratory and urinary tract infections.

A new method for the extraction of the phytopharmaceuticals contained in herbs has recently been developed. This so-called “phytoneering” from “phyto-engineering” consists of three phases: initially, the extracts are analysed by mass spectrometry to determine the component ingredients and their relative quantities; next the extracts collected are examined to find especially promising candidates, by systematically and automatically testing all extracts for their impact on cell culture systems with relevance to the disease. Finally, these findings allow for optimisation of extracts to enhance their effects. Using sophisticated separation technologies, partial extracts are produced that contain the particularly effective ingredients in higher concentrations compared with the original extract.

Sinupret® has been developed using phytoneering processes and contains extracts of five herbs: elder (Sambucus nigra), caprifoliaceous flowers, primrose (Primula veris, Primulaceae) flowers with calyx, common sorrel (Rumex acetosa, Polygonaceae), European vervain (Verbena officinalis, Verbenaceae) and gentian (Gentiana lutea, Gentianaceae) root. The flowers of the black elder act as a mucolytic. The active substances of the cowslip flowers and calyx act as mucolytic agents, have anti-inflammatory activity and combat the causes of disease: namely, viruses and bacteria. The leaves and stems of common sorrel act as mucolytic agents and have an anti-inflammatory effect. The leaves and stems of verbena also act as mucolytic agents and have antiviral activity. Gentian root contains substances with mucolytic action.

The primary outcome of our manuscript was to evaluate the efficacy and safety of this new way of extraction in the treatment of acute and chronic rhinosinusitis in children. The secondary outcome was assessment of pharmacological effects, such as anti-inflammatory or mucolytic activities, in vitro and in experimental animals.
Materials and methods

A PubMed literature search was performed in June 2014 using the following key words: “sinusitis”, “phytotherapy”, “phytomedicine” and “herbal drugs”. The additional filter selected was “Text Availability: Abstract”. The abstracts and titles obtained were screened independently by two of the authors (DP and JC) who subsequently met and discussed any divergences regarding citation insertion. The exclusion criteria were absence of the full text and the main text not being available in English or German. We also excluded reviews and articles on otitis media and bronchitis, which are beyond the scope of our review. We considered separately manuscripts that did not use the technique of extraction and processing of phytoneering, but reported data on phytotherapy and rhinosinusitis in children. All the main texts were retrieved and read by both reviewers.

Results

The initial search produced a total of 50 results using the abovementioned criteria. Twenty-two articles were eligible for inclusion. With regard to the articles on ARS, 6 articles were identified, in 4 of which patients were treated with phytoneering herbal drugs (Table I).

The studies analysed indicated that herbal drugs have mucolytic, antiviral, antimicrobial, anti-inflammatory and secretolytic activity in experimental animals. Phytotherapy in vivo has also been demonstrated to be efficacious in reducing the symptoms of acute and chronic rhinosinusitis in children and the adult population, showing a high level of tolerability and safety. Herbal products developed using phytoneering techniques have shown improvements in performance compared with previous phytotherapeutic preparations, probably because the method allows for the duplication of the individual active components contained in plant extracts, thus enhancing the final pharmacological effects.

Antimicrobial and antiviral effects

The antimicrobial effects of phytoneering herbal drugs in vitro were assessed on *Staphylococcus aureus*, methicillin resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Escherichia coli* and *Haemophilus influenzae*. A phytoneering product (Sinupret-Bionorica) has bactericidal effects on *E. coli* ². In fact, experiments performed in New Zealand on white rabbits with experimentally-induced maxillary sinusitis by *Streptococcus pneumoniae* showed that phytoneering herbal extract (300 mg/kg b.w./day) reduced bacterial counts in sinuses, as well as the obstruction, opacification and inflammation of the sinus mucosa.

The phytoneering product has antiviral effects against adenovirus C subtype 5 (Adeno 5), human rhinovirus B subtype 14 (HRV 14) and the long strain of respiratory syncytial virus (RSV), in all of which the dry extract was significantly superior to oral drops (Fig. 1) ³. In an animal study, rats and rabbits were inoculated with *Strep. pneumoniae* to provoke bacterial rhinosinusitis and then treated with the phytoneering product, which brought about a statistically significant reduction in bacterial growth after 8 days ⁴.

**Table I. Literature reports on herbal therapy in children with ARS.**

| First author | Year | Study design                  | N      | Days | Dosage                | Preparation                  | Significant findings                              | Complications               |
|--------------|------|-------------------------------|--------|------|-----------------------|------------------------------|--------------------------------------------------|-----------------------------|
| Braun        | 1990 | Randomised, open-label,       | 114    | 21   | 2 tablets 3x/d or N-acetylcysteine 200 mg 3x/d | Sinupret⁵ Tablets           | 12.3% improved, 56.1% were w/out pathologic findings | None                        |
| Kraus        | 1992 | Randomised, open-label,       | 134    | 28   | N/A                   | Sinupret⁶ Tablets           | 49% classified as “nothing abnormal detected” or “improved” | None                        |
| Neubauer     | 1994 | Randomised, placebo-controlled, double-blind | 160    | 14   | 2 tablets 3x/d or placebo | Sinupret⁷ Tablets           | Improvements from baseline on radiograms | None                        |
| Biebach      | 2004 | Open-label, multicentre       | 3109   | N/A  | 20 drops 3x/d or 1 tablet 3x/d | Sinupret⁸ Drops & Sinupret⁹ Tablets | 93% reported “little” nasal discharge or no discharge & 90% reported discharge as “thin” & “clear” | None                        |
| Braun        | 2005 | Comparative, multicentre      | 116    | N/A  | N/A                   | Bromelain-POS⁰ Tablets      | The duration of symptoms was lower                | One case of pineapple allergy |
| Goos         | 2007 | Prospective, multicentre      | 297    | N/A  | N/A                   | Angocin⁰ Anti-Infekt N vs. antibiotic | Reduction of complaint score in 84.8% vs. 85.5% | < 1% of adverse events      |
A study on mice inoculated with Sendai virus (Parainfluenza viridae) showed that preventive treatment with the phytoneering herbal drug determined a significantly longer survival time compared with placebo \((p < 0.05)\) 5.

Eucalyptus oil and its main product 1,8-cineole demonstrated antimicrobial activity against microorganisms grown in planktonic cells and biofilm. Crude eucalyptus oil was significantly more efficacious than 1,8-cineole \((p < 0.05)\) against microorganisms grown in suspensions of \textit{Staphylococcus aureus}, \textit{MRSA}, \textit{Escherichia coli} and \textit{Candida albicans}, and in biofilm cultures of \textit{MRSA} and \textit{Pseudomonas aeruginosa} 6.

Secretolytic activity

The secretolytic activity of the phytoneering herbal drug was assessed in rabbits by administering the individual herbs contained and then analysing the tracheal mucus. The phytoneering product and all the individual herbs (especially European vervain and gentian root extracts) produced a statistically significantly increase in the fluidity of secretions compared with baseline \((p < 0.05 \text{ in all cases})\) 7.

Another study evaluated the effects of the phytoneering herbal drug and its individual components on the secretion activity of rat respiratory epithelium using phenol red, demonstrating a dose-dependent effect on tracheobronchial secretion 8.

The phytoneering product extract stimulates the ciliary beat frequency of human bronchial epithelial cells, with a significant increase only 10 min post-application and dose-dependent effects lasting up to 1 hour (Fig. 2). The extract has also been shown to stimulate transepithelial \(\text{Cl}^-\) transport 9.

Anti-inflammatory activity

The immunological role of the Sinupret (the phytoneering Herbal grug) has been examined in human leukocytes in vitro. The gentian root extract and vervain extract increased the phagocytic activity of neutrophils, while sorrel inhibited phagocytosis at high concentrations. At low concentrations it augmented phagocytosis, but only marginally. High concentrations of phytoneering product slightly stimulated the proliferation of lymphocytes in vitro 10.

The phytoneering herbal drug was evaluated in rats in which inflammation was provoked in the lower extremities. It reduced itchy red wheals and the highest dose tested was as successful as phenylbutazone 7.

The efficacy against bacterial infections of the upper airways was tested in mice inoculated intranasally with \textit{Strep. pneumoniae} to induce bacterial rhinosinusitis. It significantly reduced bacterial growth \((p < 0.01)\) and the amount of goblet cells (cells that secrete mucous) \((p < 0.05)\), and also improved the quality of secretions compared with controls \((p < 0.01)\) 11.

Anti-inflammatory action has also been demonstrated in rats with induced pleural inflammation. The rats in which the phytoneering product was administered orally one hour before treatment (which caused inflammation after 4 hours) showed a lower volume of pleural effusion, less infiltration of polymorphonuclear leukocytes and decreased formation of \(\text{PGE}_2\) in the exudates, as well as lower quantities of cyclooxygenase (COX)-2 protein in the lungs (Fig. 3) 12.

The anti-inflammatory activity of 1,8-cineole was evaluated in rats with carrageenan-induced inflammation or a cotton pellet-induced granuloma, and an inhibitory effect was demonstrated against these two types of experimental inflammation. In mice, an oral dose of 400 mg/kg of 1,8-cineole has been shown to inhibit the acetic acid-induced increase in peritoneal capillary permeability and the chemical nociception induced by intraplantar formalin and intraperitoneal acetic acid 13.

The anti-inflammatory activity of bromelain has recently been demonstrated through changes in circadian cytokine profiles. A significant shift in the circadian profiles of the
Th1 cell mediator interferon gamma (p < 0.043) was demonstrated after administration of 3000 units of bromelain, and similar trends were shown in the profiles of the Th2-type cytokine IL-5 as well as the immunosuppressive cytokine interleukin (IL)-10. This suggests a general effect on the antigen-specific (T cell) compartment of the human immune system 14.

**Acute rhinosinusitis (ARS)**

A randomised, placebo-controlled, double-blind trial was conducted in 160 subjects (mean age 24.5 years) with acute bacterial sinusitis (opaque sinus radiographs at baseline) who were receiving antibiotic (vibramycin) and decongestant (orificin) therapy, adding either Sinupret® or placebo tablets. Compared with placebo-treated patients, significantly more patients in the phytoneering product group showed improvements from baseline in radiographs (p = 0.008). These patients also reported improvements in mucosal swelling, nasal obstruction and headache. The authors concluded that the phytoneering herbal drug can improve basic (i.e. conventional drug) therapy 15.

In children with ARS, phytoneering product in two formulations (drops and tablets) evaluated in 1639 girls and 1471 boys (mean age 6.9 years). The dosage varied according to the patients’ age. Two-thirds (64%) of subjects took an average of 20 drops 3 times per day, while the others took tablets. At baseline, the most frequently found symptoms were “abundant” and “viscous” nasopharyngeal discharge, impaired nasal breathing and “moderately severe” cough.

At the final check-up (after an average of 12 days’ treatment), 93% of children reported “little” nasal discharge or no discharge and 90% reported the discharge as “thin” and “clear.” At the study end, only 0.3% of children reported severe impairment of nasal breathing and 75% had no cough. The symptoms “blocked nasal breathing”, “headache”, “hoarseness” and “cough” clearly improved with the phytoneering product in both age groups and with both formulations. Nearly 90% of physicians involved assessed the efficacy of the phytoneering herbal drug as very good or good.

However, in 2-6-year-old children the sugar coated tablets were slightly superior to the drops in treating stuffy noses and coughs, while the drops were more effective at improving facial pain and headache (Fig. 4) 16.

The major limitation of this study was that there was no placebo group or untreated control group. Acute rhinitis is often a self-limiting syndrome, so that a control group is necessary in such studies. Further limitations were the variable dosing, lack of information about the treatment period, and large percentage of the patients (74%) taking concomitant cold/flu medication, such as rhinological agents and/or antibiotics.

A randomised, open-label, comparative study was conducted in 134 patients with radiologically diagnosed ARS. All subjects were treated for 3 weeks with phytoneering sugar-coated tablets. After 3 weeks of treatment, 49% of patients were reported as having “nothing abnormal detected” or “improved” 17. A limitation of the study was the lack of an untreated or placebo control group. It is unclear whether the 49% of patients showed improvements at 3 weeks due to the treatment or if rhinosinusitis resolved spontaneously.

A further randomised, open-label, comparative study was conducted in 114 patients with radiologically (X-ray) diagnosed ARS. All subjects were treated for 21 days with the phytoneering sugar-coated tablets. After 21 days of treatment, X-ray examination revealed that 12.3% (7/57) of phytoneering herbal drug-treated patients had improved and 56.1% (32/57) were without pathological findings. Approximately 85% of these subjects reported that they were “improved” or “cured” 18. This study was also limited by the need for an untreated or placebo control group. Moreover, the researchers permitted the use of associated drugs, which could have affected the outcome.
A multicentre randomised, double-blind, placebo-controlled study was conducted in 386 adult patients with acute viral rhinosinusitis diagnosed radiologically (ultrasonography). One hundred and ninety subjects were treated with 160 mg phytoneering herbal product three times a day for 15 days with a mean follow-up of 14 days. The major symptom score (rhinorrhea, post nasal drip, nasal congestion, headache and facial pain) after 15 days was statistically significantly lower in the phytoneering herbal drug group, with 48.4% of patients considered cured. After treatment, ultrasonography showed 73.2% of patients treated with herbal drug were without pathological findings (vs. 61.6% in the placebo-treated group) 19.

The activity of bromelain in children with ARS was evaluated in a trial involving 62 patients. The duration of symptoms was lower if patients were treated with only bromelain extract compared with standard therapy or combination therapy (6.66 vs. 7.95 vs. 9.06 days until resolution of symptoms, respectively) 20.

A prospective cohort study was performed involving 297 children with ARS treated with Angocin® Anti-Infekt N or with a standard antibiotic, according to the physician’s decision. At the end of treatment, the reported symptoms were reduced by 84.8% vs. 85.5% in the antibiotic group. However, the study contained major limitations: prior to treatment symptoms in the Angocin® group were significantly less severe than those of the antibiotic group. Moreover, no standard protocol for treatment was used, being left to the judgment of the physician 21.

Two randomised double-blind, placebo-controlled trials were conducted on populations of adults (n = 29 and n = 99) with ARS using Cyclamen europaeum extract. In the first study, after seven days of treatment, intranasal, lyophilised, reconstituted Cyclamen europaeum extract significantly reduced sinus opacification compared with placebo treatment on CT scans, and reduced the total symptom scores from baseline 22. The second study, on the other hand, did not show significant differences in total symptom scores after 7 days, but only a reduction in facial pain and an improvement in endoscopically-assessed mucosal obstruction 23.

The activity of 1,8-cineole was demonstrated in a randomised, double-blinded controlled study on 75 patients with ARS. After a treatment period of 7 days, cineole brought about a statistically significant reduction in total symptom scores (11.0 ± 3.3 vs. 8.0 ± 3.0) 24.

A randomised double-blind, placebo-controlled trial was conducted on populations of 152 adults with acute non-purulent rhinosinusitis. A dose of 600 mg of cineole daily was administered. After 4 and 7 days, the symptoms-sum-score was significantly lower in treatment group 25.

Kan Jang® was evaluated in 95 patients with acute upper respiratory tract infections and showed significant improvements after 5 days in headache, nasal and throat symptoms, even in the sinusitis subgroup of this clinical study 26. Roots of Pelargonium sidoides were compared to placebo in a randomised double-blind trial on 103 adults with acute rhinosinusitis. The sinusitis severity score after 7 days of treatment confirmed that the therapy was well tolerated with a decrease of 5.5 points 27.

**Chronic rhinosinusitis (CRS)**

A randomised, double-blind, placebo-controlled trial was conducted on 31 patients with CRS. Radiological results of the paranasal sinuses showed that 12/16 of the phytoneering herbal drug-treated patients experienced considerable improvements or total recovery compared with 6/15 placebo-treated patients (p value not reported). Treatment with phytoneering product showed a significant improvement in headache (p = 0.025) and in paranasal sinuses at X-ray (p = 0.001). The authors concluded that phytoneering components had a positive effect on subjective and objective findings in patients with chronic sinusitis 28. Although this study was limited by its small size, the objective measures provide credibility to support its conclusions.

A randomised, open-label, comparative study was conducted on 46 patients experiencing an exacerbation of CRS, as diagnosed radiologically. Seventeen subjects were treated for 21 days with phytoneering herbal tablets (2 tablets, 3 times per day). X-ray examination revealed that 23.5% (4/17) of the phytoneering product-treated patients improved and 41.7% (10/24) were without pathologic findings. The authors concluded that phytoneering drug was equivalent to N-acetylcysteine therapy 18. This study was limited by the need for an untreated or placebo control group. In addition, the researchers permitted the use of associated drugs, which could have modified the outcome.

**Discussion**

The value of Sinupret® has been evaluated by many researchers. This preparation is the only one to use the phytoneering technique of production, which allows for greater concentration and purification of the herbal active ingredients. This review of clinical findings has shown that Sinupret® is helpful in enhancing the results of pharmaceutical therapy. However, preliminary results evaluating the efficacy of Sinupret® in the treatment of chronic rhinosinusitis are ambiguous and larger prospective studies are needed.

Considering the primary outcome of efficacy and safety in the treatment of acute and chronic rhinosinusitis in children, herbal medicine can be considered as a viable ancillary therapy, as it is well tolerated by patients and not disdained by families or paediatricians. Various studies have reported improvements in subjective symptoms associated with ARS, such as nasal obstruction and head-
ache, as well better recovery by radiographic examination and in nasal mucosal swelling. Regarding the secondary outcome of safety, Sinupret® does have pharmacological effects, as demonstrated by research in vitro and in experimental animals. The effects that correlate with a potentially helpful role in the treatment of ARS in children are the antiviral and antimicrobial effects of Sinupret® and 1,8-cineole, and the anti-inflammatory and secretolytic effects of Sinupret® and bromelain.

Although until now herbal therapy was considered to be an ancillary therapy for adult population with viral and postviral ARS, it is useful in reducing the duration of symptoms and the use of standard therapies. Herbal compounds have been commonly used in treatment of ARS, but only a few double-blind, placebo-controlled, randomised studies have shown their efficacy. However, the available data with herbal medicines prepared using the phytoneering technique of production encourage the use of this therapy in children with viral ARS as they are free of side effects and helpful in reducing the duration of symptoms and days of standard therapies. Hence, the benefit of herbal compounds in treatment of ARS need to be confirmed by more well designed and randomised clinical trials.

Conclusions

The current literature suggests that phytotherapy is an effective and safe ancillary treatment for RS in children. In particular, herbal medicines prepared with the technique of phytoneering (Sinupret®) have proven effective for acute rhinosinusitis treatment. This preparation technique proved to be superior compared with previous production methods for isolation, synthesis and duplication of the active components contained in herbs.

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