

Complementary and Integrative Treatments Rhinosinusitis

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KEYWORDS

- Rhinosinusitis • Sinusitis • Integrative medicine • Traditional Chinese medicine
- Complementary and alternative medicine • Herbal medicine • Acupuncture

KEY POINTS

- Rhinosinusitis is characterized by inflammation of the mucosa involving the paranasal sinuses. It is one of the most common and significant health care problems in the United States.
- Evidence demonstrates that antibiotics provide very little clinical benefit and that although most patients will experience improvement following endoscopic sinus surgery, a significant proportion will not.
- The goals of treatment are to improve drainage, remove obstruction, promote mucociliary function, eradicate infection, reduce inflammation, and prevent complications.
- There is evidence for beneficial integrative treatment using herbal supplements, especially for *Pelargonium sidoides*, Sinupret, and Sinfrontal.
- There is evidence for beneficial integrative treatment using traditional Chinese medicine, including acupuncture and Chinese herbal medicine (*Xanthii fructus* and *Flos magnoliae*).

OVERVIEW

Rhinosinusitis (RS) is characterized by inflammation of the mucosa involving the paranasal sinuses and the nasal cavity and is the preferred term for sinusitis because this is almost always accompanied by concurrent nasal airway inflammation.^{1,2} It is one of the most common and significant health care problems in the United States, with approximately 31 million Americans affected annually, prompting nearly 13 million physician office visits and more than 600 000 ambulatory surgical procedures per

Disclosure: The authors have no relevant financial interests pertaining to this article.

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Otolaryngol Clin N Am 46 (2013) 345–366

<http://dx.doi.org/10.1016/j.otc.2013.02.002>

0030-6665/13/\$ – see front matter Published by Elsevier Inc.

oto.theclinics.com

year.³⁻⁶ Quality of life can be adversely impacted, and emotional and daily functioning can be significantly impaired.^{7,8} It is estimated that direct health care costs of more than \$8.6 billion and indirect costs of approximately 73 million days of restricted activity are incurred annually.^{9,10}

RS is the fifth leading diagnosis treated with antibiotics, with 21% of adults receiving prescriptions for this condition.¹¹ Despite this, an increasing amount of evidence demonstrates that antibiotics provide very little clinical benefit, with an average adverse event rate of 15% to 40% among different classes of antibiotics and severe adverse events in 3.5% of patients.¹²⁻¹⁵ The enormous use of antibiotics can also contribute to the emergence of antibiotic-resistant bacteria.^{16,17} Surgical interventions are used when patients have failed to respond appropriately to medical therapy. However, although most patients will experience improvement in symptoms and quality-of-life measures following endoscopic sinus surgery, a significant proportion (nearly 30%) will not, particularly those undergoing revision surgery.¹⁸

The causes of RS include infectious and allergic components but also involve environmental, general host, and local anatomic factors. Psychiatric conditions, such as depression, have also been found to be significant factors in the outcomes of patients treated with chronic RS.^{19,20} Current standard treatment modalities commonly use multiple therapeutic methods to break the cycle of chronic disease. However, to date, there is no consensus as to the optimal treatment algorithm for patients with chronic RS.²¹ Success in the treatment of chronic RS, unlike in acute RS, is variable and prone to relapse. Therefore, it is important to find other safe and effective treatments of RS.

There has been an explosion in the use of complementary and integrative medicine (CIM) in general over the last few decades; more than a third of Americans use some form of CIM, with annual out-of-pocket expenditures estimated to exceed \$27 billion.²²⁻²⁴ Surveys have also demonstrated that there is an increasing amount of interest in the use of CIM modalities specifically for the treatment of RS both in the United States²⁵⁻²⁸ and internationally.²⁹⁻³¹ This finding seems to be true along the continuum of care for RS, whether before seeing an otolaryngologist or after aggressive medical and surgical therapy. There is also a wide range of therapies sought, including herbal medicine, acupuncture, homeopathy, and massage.

This article focuses on an integrative approach to RS.

PHYSIOLOGY AND ANATOMY

Diagnosis

RS can be categorized by duration of symptoms: acute (up to 4 weeks), subacute (4-12 weeks), and chronic (more than 12 weeks). Acute RS can be further categorized into viral RS or acute bacterial RS, with 4 or more episodes per year described as recurrent acute bacterial RS.^{2,32-35}

Anatomy

The boundaries of the nasal cavity are the cribriform plate superiorly and the palatine processes of the maxilla inferiorly. Located on the lateral wall of the nose are the inferior, middle, superior turbinates, and, in some individuals, the supreme turbinates. The ostia for the anterior ethmoid sinuses and maxillary sinuses are beneath the middle turbinate, whereas the nasolacrimal duct opens beneath the inferior turbinates. The sphenoid ostium is located between the posteromedial border of the superior turbinate and the nasal septum. The nasal septum divides the nasal cavity and is comprised of both cartilage and bone and lined by respiratory mucosa.

The paranasal sinuses are comprised of 4 paired sinuses: maxillary, ethmoid, sphenoid, and frontal. The roof of the ethmoid sinus is the fovea ethmoidalis, which forms the floor of the anterior cranial cavity and slopes upward at an angle from the midline to extend 2 to 3 mm above the cribriform plate. The lateral wall of the ethmoid is the lamina papyracea, which is also the medial wall of the orbit. The ethmoid sinuses are comprised of numerous small air cells, which develop from evaginations of the lateral nasal wall in the embryo. There are an average of 9 ethmoid air cells present, although the number varies widely.

The ethmoid sinus can be divided into anterior and posterior groups of air cells. The anterior group of ethmoid cells includes the frontal recess, bullar, and infundibular cells. The infundibulum is the site of drainage for the frontal sinus and anterior ethmoid cells and is located lateral to the middle turbinate and anterior to the bulla. The bullar cells drain into the middle meatus via the hiatus semilunaris, a large cleft in the lateral nasal wall. The uncinat process, which forms the anterior border of the hiatus semilunaris, is a ridge of bone extending from the ascending process of the maxilla. The remaining anterior ethmoid cells drain into the middle meatus, whereas the posterior cells drain into the sphenoidal recess. The vascular supply for the ethmoid sinuses is from the anterior and posterior ethmoidal arteries, and innervation of the sinuses comes from the orbital division of the fifth cranial nerve.

The maxillary sinuses are roughly triangular in shape, with boundaries of the orbital floor superiorly, the lateral nasal wall medially, and the bony lateral wall. The sinus drains into the natural ostium on the superior medial wall, which flows into the hiatus semilunaris. There may also be accessory maxillary sinus ostia in the medial sinus wall.

The frontal sinus originates from the frontal recess cells of the anterior ethmoid and at birth is often indistinguishable from these cells. The frontal sinus is usually well formed by 12 years of age but does not reach adult size until 18 to 20 years of age. The anterior table is twice as thick as the posterior table when measured in the midsagittal plane inferiorly. An intersinus septum separates the two sinuses. The sinuses drain through a nasofrontal recess into the hiatus semilunaris beneath the middle turbinate. In most adults, this recess is a mucous membrane-lined bony canal measuring 3 mm or greater.

The ostiomeatal complex includes the middle turbinate, uncinat process, middle meatus, hiatus semilunaris, and infundibulum. The drainage pathways for the frontal, anterior ethmoid, and maxillary sinuses all flow through the ostiomeatal complex. Obstruction of this relatively narrow path from polyps or other mass lesions, inflammatory edema, or purulence will result in postobstructive sinusitis involving one or more of the aforementioned sinuses.

The sphenoid sinuses originate as evaginations from the sphenoidal recess. They are present at birth but do not begin to pneumatize until about 3 years of age. The development of the sinuses may continue through adulthood, and the size may vary greatly because of differences in the degree of development. The midline is often an irregularly shaped intersinus septum. Drainage is into the sphenoidal recess medial to the superior turbinate. The superior boundary is the sella and pituitary fossa, whereas the lateral walls contain the optic nerve, carotid artery, and cavernous sinus. There may be bony dehiscence of the lateral wall over these structures.

Histology

The paranasal sinuses are lined by respiratory epithelium, which consists of pseudostratified ciliated columnar epithelium with goblet cells. Numerous mucous and seroanguinous glands are present. In addition to mucus, the sinus glands also secrete

immunoglobulins, interferons, and lysozyme. The anterior portion of the nares and nasal septum are covered by skin with adnexa. The roof of the nasal cavity contains specialized olfactory epithelium with bipolar olfactory neurons.

Physiology

The sinus epithelium forms a mucociliary system, which supplies the nose with a mucous covering to warm and humidify inspired air. Both parasympathetic and sympathetic nerves supply this mucous blanket, which is renewed every 10 to 15 minutes.^{36,37} The cilia beat 10 to 15 times per second and move the mucous blanket toward the natural ostia of the sinuses. Environmental factors influence ciliary function; humidity increases the activity, whereas dehydration and cold temperatures decrease flow.³⁸ Bacterial and viral proliferation may increase when there is dysfunction of the cilia and relative stasis of the mucous blanket. In addition to mucociliary dysfunction, any condition that obstructs the drainage of the sinuses (eg, polyps, inflammation, or edema of the nasal mucosa) will lead to sinusitis. Benign and malignant tumors of the nasal cavity, paranasal sinuses, and skull base can also lead to a postobstructive sinusitis of one or more of the paranasal sinuses.

Pathophysiology

A variety of host and environmental factors play a role in the development of RS. Host factors can be divided into general (genetic factors and immune deficiency), local (anatomic abnormalities, mucosal and bone inflammation), and environmental factors (air pollution, smoke, allergens, viruses, bacteria, and fungi).³⁹ The pathophysiology leading to RS of the maxillary and frontal sinuses usually involves a constellation of changes that lead to the obstruction of the ostiomeatal complex, including mucosal swelling and inflammation, mucous stasis, impaired mucociliary function, and microbial infection.

Lately, several different theories have emerged to describe the pathophysiology involved in chronic RS, especially of a recalcitrant nature, including inflammation, fungal-mediated hypersensitivity, bacterial biofilms, osteitis, and superantigens, with novel therapies targeted toward each of these specific areas.^{40–46}

Other conditions to consider that can mimic chronic RS include gastroesophageal reflux disease, adenoiditis, Thornwaldt cyst, dental infection, granulomatous disorders, and neoplasia.⁴⁷

SYMPTOMS

The signs and symptoms of RS can differ depending upon contributing factors and the overall duration. Acute RS often presents with purulent nasal discharge with nasal obstruction and facial pain or pressure. Additional symptoms can include hyposmia/anosmia, headache, fever, cough, aural fullness, halitosis, fatigue, and dental pain.³² Because purulent nasal discharge cannot be used as a sole factor to distinguish between viral and bacterial infection, the illness pattern and duration should be used instead, with viral RS usually lasting less than 10 days, but acute bacterial RS being more persistent.^{2,48} Chronic RS exists if these symptoms continue for greater than 12 weeks.

MEDICAL TREATMENT APPROACHES

The goals of treatment are to improve drainage, remove obstruction, promote mucociliary function, eradicate infection, reduce inflammation, and prevent complications.

Medical therapies for RS can include any of the following: intranasal or systemic steroids, topical or oral antibiotics, nasal saline irrigation, topical or systemic decongestants, antihistamines, leukotriene antagonists, mucolytics, expectorants, immunotherapy, and analgesics. If these conventional therapies are not effective and symptoms become refractory, other medical options that have been used include antifungals, proton-pump inhibitors, bacterial lysates, immunomodulators, and immunostimulants.^{47,49–52} Long-term, low-dose macrolide therapy may also have a role in the treatment of chronic RS, given its demonstrated antiinflammatory effects.^{53–55}

SURGICAL TREATMENT APPROACHES

Endoscopic sinus surgery is indicated for 2 reasons: (1) failed medical treatment or (2) potential or actual complications, such as the development of a mucocele, mucopyocele, orbital abscess, invasive fungal sinusitis, anatomic obstruction caused by polyps or mass lesion, or suspicion of malignancy. Substantial evidence exists that supports surgical intervention in reducing symptoms and improving quality of life in patients with RS.⁵⁶

INTEGRATIVE TREATMENT APPROACHES AND OUTCOMES

Herbal Supplements (Single)

***Pelargonium sidoides* EPs 7630**

In South Africa, *Pelargonium sidoides* (*P. sidoides*) has historically been used to treat a variety of ailments, including upper respiratory tract infections like bronchitis and tuberculosis.⁵⁷ *P. sidoides*, traditionally known as Umckaloabo, is rich in phenols and flavonoids, consisting of coumarins, tannins, diterpenes, and proanthocyanidins.^{58–60} It has been standardized in Germany as an aqueous ethanolic extract of its root known as EPs 7630.

EPs 7630 has been shown to have significant antibacterial activity against multiresistant *Staphylococcus aureus* and antiviral effects against seasonal influenza A virus strains (H1N1, H3N2), respiratory syncytial virus, human coronavirus, parainfluenza virus, and Coxsackie virus.^{58,61} Through its immunomodulatory effects, EPs 7630 has been demonstrated to specifically enhance human peripheral blood phagocyte activity as well as have antiadhesive effects through interaction with bacterial surface binding factors.^{62–64}

A double-blind, randomized, multicenter trial conducted by Bachert and colleagues⁶⁵ enrolled 103 patients with radiographically and clinically confirmed acute RS and compared EPs 7630 (1:8–10; extraction solvent: ethanol 11% at a dosage of 60 drops 3 times daily for up to 22 days) with placebo. EPs 7630 was found to have superior efficacy and tolerance, based on changes in sinusitis severity scores. A Cochrane review concluded that *P. sidoides* may be effective in alleviating symptoms, including headaches and nasal discharge, for acute RS and the common cold in adults.⁶⁶

Bromelain

Bromelain, a mixture of proteolytic enzymes extracted from pineapples (*Ananas comosus*), has demonstrated antiinflammatory, antiedematous, antithrombotic, and fibrinolytic effects.⁶⁷ Three double-blind, randomized controlled trials were conducted in the 1960s on patients with acute and chronic RS, using similar protocols of 2 parallel treatment arms comparing bromelain with placebo, with each group also receiving conventional management consisting of antibiotics, decongestants, antihistamines, and analgesics.^{68–70} A meta-analysis performed by Guo and colleagues⁷¹ showed

a small but statistically significant difference in favor of adjunctive treatment with bromelain for nasal mucosal inflammation, nasal discomfort, breathing difficulty, and overall rating but not for nasal discharge.

A recent multicenter trial enrolling children less than 11 years of age with acute sinusitis had 3 treatment groups (bromelain vs bromelain + standard therapy vs standard therapy) and showed a statistically significant recovery time with bromelain monotherapy compared with other treatment groups.⁷² Only one mild self-limiting allergic reaction was noted. The 1993 German Commission E monograph concluded that bromelain may be effective for “acute postoperative and post-traumatic swelling, especially of the nose and paranasal sinuses.”⁷³

Caution must be used when prescribing bromelain for patients already on anticoagulants because of the increased risk for bleeding as well as when prescribing various antibiotics, such as penicillin and tetracycline, because bromelain is also known to promote their absorption.⁶⁷ Moreover, bromelain strongly inhibits human cytochrome P450 2C9 (CYP2C9) activity and can, thereby, affect metabolism of its substrates.⁷⁴ Recommended dosages range from 500 to 2000 mg/d.⁷⁵

Cineole

Cineole, or more specifically 1,8-cineole, is a monoterpene present in many plant-based essential oils and is commonly derived from *Eucalyptus globulus*; 1,8-cineole is also one of the main chemical ingredients identified in the Chinese herb *Flos magnoliae*.⁷⁶ It has been shown to enhance mucociliary clearance; block inflammation through inhibiting formation of cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin-1beta; and activate antinociceptive properties, perhaps through a mechanism involving a nonopioid receptor.⁷⁷⁻⁷⁹

A prospective, randomized, double-blind study comparing cineole (200 mg 3 times per day) with placebo in 152 patients with acute nonpurulent RS showed a statistically significant difference in symptoms sum scores in the cineole group, in addition to a reduction in secondary symptoms, such as headache on bending, frontal headache, nasal obstruction, and nasal secretion.⁸⁰ Mild side effects, including heartburn and exanthema, were noted with cineole. The investigators concluded that cineole may serve as an integrative therapy during the first 4 days of acute RS, but antibiotics should be initiated if symptoms persist. In addition, another prospective, randomized, double-blind study demonstrated that cineole was more effective than an herbal preparation with 5 different components in the treatment of acute viral RS.⁸¹

Cod liver oil

Cod liver oil, which is rich in omega-3 fatty acids and vitamin D, was historically used as a remedy for rickets in the 1800s.⁸² There is limited evidence for the use of cod liver oil for RS, including a 4-month, open-label study enrolling 4 children with recurrent chronic RS who were given escalating doses of cod liver oil and a multivitamin with selenium.^{83,84} Three patients demonstrated a positive response with decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer physician visits. The investigators concluded that cod liver oil in combination with a multivitamin containing selenium was an inexpensive, noninvasive adjunctive intervention that can be used for selected patients.

Manuka honey

Manuka honey is produced from the nectar of flowers native to Australia and New Zealand, particularly from the species of *Leptospermum*, and has potent antibacterial activity attributed to its high concentration of methylglyoxal, hyperosmolarity, hydrogen peroxide, and low pH.^{85,86} It was found to have bactericidal activity against

biofilms formed by *Pseudomonas aeruginosa* and *Staphylococcus aureus*, with significantly higher effects than commonly used antibiotics and may have implications for treating chronic RS.^{87,88}

Thamboo and colleagues⁸⁹ studied the use of manuka honey in patients with allergic fungal RS. Thirty-four patients were treated with a topical combination of manuka honey and saline in one nostril daily for 30 days. Culture results from their ethmoid cavities were unchanged, as was their endoscopic staging. However, there was reported symptomatic improvement using the Sino-Nasal Outcome Test (SNOT)-20 as an outcome measure.

Herbal Supplements (Combination)

Sinupret

Sinupret (comprised of *Gentiana radix*, *Primula flos*, *Rumex herba*, *Sambucus flos*, and *Verbena herba*) is an herbal formula used widely in Germany for the treatment of respiratory infections. Approved by the German Commission E in 1994 for the treatment of acute and chronic inflammation of the paranasal sinuses, Sinupret is available as a coated tablet of 6 mg of *Gentiana radix* and 18 mg each of *Primula flos*, *Rumex herba*, *Sambucus flos*, and *Verbena herba* or as a water and alcohol extract in a proportion of 1:3:3:3:3.⁷³

Sinupret has been shown to have antiviral activity in vitro against certain subtypes of viruses known to cause respiratory infections, including adenovirus, human rhinovirus, and respiratory syncytial virus and to strongly stimulate transepithelial Cl(-) secretion to maintain normal mucociliary clearance in sinonasal epithelium through the hydration of the airway surface liquid.^{90,91}

Four randomized controlled trials (RCTs) evaluated Sinupret (either 2 tablets or 30 drops of liquid formula 3 times per day) as adjunctive therapy for acute RS (3 RCTs) and chronic RS (1 RCT) (Berghorn, Langer W, März RW, Bionorica GmbH, unpublished data, 1991).⁹²⁻⁹⁴ A systematic review demonstrated that Sinupret may be effective as an adjunctive therapy in acute RS.⁷¹ However, one study found no significant difference in olfactory function between patients treated with Sinupret versus placebo, although an initial therapy of oral prednisolone for 7 days had preceded the treatment intervention.⁹⁵

Esberitox

Esberitox is an herbal extract containing *Thuja occidentalis* (white cedar), *Echinacea purpurea* and *pallida* (purple coneflower), and *Baptisia tinctoria* (wild indigo) with demonstrated immunomodulatory properties.⁹⁶

A randomized, double-blind, placebo-controlled study showed a dose-dependent efficacy in the treatment of upper respiratory infections and, in particular, certain symptoms like rhinorrhea.⁹⁷ Another study that enrolled 90 patients with acute RS compared (1) Esberitox (3 tablets 3 times per day) and doxycycline, (2) Sinupret (5 tablets twice per day) and doxycycline, and (3) doxycycline alone and found that both groups with combination therapies had a significantly higher rate of response.^{71,94} Reported adverse events included photosensitivity and gastrointestinal symptoms, such as nausea.

Myrtol

Myrtol is a standardized phytotherapeutic extract (Gelomyrtol/Gelomyrtol Forte) taken from *Pinus spp*, *Citrus aurantifolia*, and *Eucalyptus globulus*. It is mainly comprised of 3 monoterpenes: (+) alpha-pinene, D-limonene, and 1,8-cineole. It has been shown to inhibit 5-lipoxygenase activity as well as various mediators of the inflammatory and allergic response, including leukotriene C4 and prostaglandin E2.⁹⁸

In a randomized, double-blind, multicenter trial, 330 patients with acute sinusitis were enrolled into one of 3 arms: (1) Myrtol extract (300 mg/d), (2) other unidentified essential oil, or (3) placebo.⁹⁹ Myrtol and the other essential oil groups both demonstrated superior efficacy to placebo based on the total symptom score of 7 items (headache, nasal secretion, nasal obstruction, pain on pressure, pain at bending over, general well-being, and fever), although there were insufficient statistical data to support this conclusion.⁷¹ Mild to moderate adverse events that were mostly gastrointestinal in nature were reported.

Nasturtium and horseradish root

Nasturtium (Tropaeoli majoris herba) and horseradish root (*Armoracia rusticanae radix*) have broad antibacterial activities against several gram-positive and gram-negative organisms, including *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pyogenes*.¹⁰⁰

A prospective, multicenter, cohort study performed in children between 4 and 18 years of age with acute RS found that an herbal drug preparation, containing nasturtium and horseradish root, had similar efficacy and fewer adverse events compared with standard antibiotics.¹⁰¹

Nutrition: Ginger, Quercetin, and Epigallocatechin Gallate

Dietary polyphenols are widely available in food and well-known for their antiinflammatory effects. Both ginger and quercetin, a polyphenolic bioflavonoid commonly found in apples and onions, have potent antioxidant and antiinflammatory properties.^{102,103} Mechanisms of action that have been elucidated for quercetin include suppression of the inflammatory mediator cyclooxygenase-2, inhibition of histamine release through downregulation of mast cell activity, and enhanced mucociliary clearance through augmented transepithelial chloride secretion via the cystic fibrosis transmembrane conductance regulator anion channel.^{104–106}

A combination of ginger extract and green tea (*Camellia sinensis*), which is rich in epigallocatechin gallate (EGCG), showed significant anti-allergy effects through the suppression of certain cytokines, such as TNF- α and MIP-1 α (macrophage inflammatory protein).¹⁰⁷ The dietary polyphenols of [6]-gingerol, quercetin, and EGCG were found to effectively inhibit excess mucus secretion of respiratory epithelial cells while maintaining normal nasal ciliary movement.¹⁰⁸

Homeopathy

Homeopathy, initially developed by German physician Samuel Christian Hahnemann at the end of the eighteenth century, is based on the principle of similars (like cures like) whereby therapeutic effects are achieved by stimulating the body's homeostatic healing response via substances that have been serially diluted and shaken. There is evidence from RCTs that homeopathy may be effective for the treatment of influenza and allergies.¹⁰⁹ In a recent prospective observational trial from Germany, 134 adult patients with treatment refractory chronic sinusitis were tried on different homeopathic remedies. Over the course of 8 years, the investigators found sustained improvements in quality-of-life outcomes (36-Item Short Form Health Survey) and decreased use of conventional medications, with the greatest change noted during the first 3 months of follow-up.¹¹⁰

Sinfrontal

Sinfrontal is a homeopathic remedy (containing *Cinnabaris* D4, *Ferrum phosphoricum* D3, *Mercurius solubilis* D6) that is commonly used in Germany for a variety of upper respiratory tract infections and has shown promise as a treatment for RS without

the need for antibiotics. A prospective, randomized, double-blind, placebo-controlled, multicenter, clinical trial comparing Sinfrontal with placebo in 113 patients with radiography-confirmed acute maxillary sinusitis found that there was a significant difference in patients treated with Sinfrontal with no recurrence of symptoms 8 weeks after treatment.¹¹¹ Patients receiving Sinfrontal were instructed to take 1 tablet every hour until improvement was noted, with a maximum of 12 tablets per day, after which the dosing would change to 2 tablets 3 times per day. An economic analysis demonstrated that Sinfrontal can lead to substantial cost savings with markedly reduced absenteeism from work.¹¹²

Traditional Chinese Medicine

Traditional Chinese medicine (TCM) is a whole medical system that has been used for several millennia. The therapeutics used in TCM, such as Chinese herbal medicine and acupuncture, have grown in popularity with a parallel increase in scientific understanding and elucidation of mechanisms.¹¹³ Specifically, the use of TCM for the treatment of disorders involving the ears, nose, and throat can be traced back as early as the fifth century BC, with several therapies that may be beneficial for RS.¹¹⁴

Acupuncture

The therapeutic effects of acupuncture primarily stem from reestablishing homeostasis of multiple physiologic cascades, whether through modulation of the immune system, inflammatory response, autonomic nervous system, neuroendocrine axis, limbic system, or pain pathway.^{115–120} Although acupuncture may modulate many of these cascades during treatment of patients with RS, specific effects of improved mucociliary clearance and airway surface liquid have also been demonstrated.¹²¹

In a prospective randomized study, patients with nasal congestion and hypertrophic inferior turbinates were treated with acupuncture and found to have significant improvement on visual analog scale and in nasal airflow as measured by active anterior rhinomanometry.¹²² Another study demonstrated a 60% reduction in sinus-related pain compared with only 30% in the placebo group.¹²³ Acupuncture also demonstrated beneficial results in the treatment of children with chronic maxillary sinusitis.¹²⁴

A research team in Norway conducted 2 different studies using a similar protocol, whereby 65 patients with chronic RS were randomized into 3 arms: (1) traditional Chinese acupuncture, (2) sham acupuncture, or (3) conventional medical management with antibiotics, oral steroids, nasal saline irrigation, and local decongestants.^{125,126} In both studies, there was improvement in health-related quality-of-life symptom scores in all 3 groups, although there was no overall statistically significant difference among them.

Chinese herbal medicine

Xanthii fructus (Chinese herbal name: Cang Er Zi) and *Flos magnoliae* (Chinese herbal name: Xin Yi Hua) are commonly used herbs in traditional Chinese medicine to treat RS. *Xanthii fructus* is also known as *Xanthium sibiricum* because the former is simply the fruit of the latter. From a TCM perspective, *Xanthii fructus* disperses wind and dampness and treats thick, viscous nasal discharge and sinus-related headaches, whereas *Flos magnoliae* is used to expel wind-cold and treat nasal discharge, hyposmia, sinus congestion, and headaches.¹²⁷ In fact, these two herbs are often combined and are key components of the Chinese herbal formula Cang Er Zi Wan or Cang Er Zi San, which are the pill and powder preparations, respectively.¹²⁸

It is important to note that Chinese herbs should be used under the guidance of TCM theory. When Chinese herbs are not used according to TCM principles, severe

adverse events can occur. One such example was the inappropriate use of Ephedra (Chinese name: Ma Huang) for weight loss, increased energy, and performance enhancement, when traditionally this is used only for upper respiratory infections for a short period of time, much like how pseudoephedrine is used only briefly for symptoms related to upper respiratory infections.¹²⁹

***Xanthii fructus* (Chinese name: Cang Er Zi)**

In a murine model, *Xanthii fructus* was found to exhibit (1) antiinflammatory effects through inhibiting interferon-gamma, TNF-alpha, and lipopolysaccharide-induced nitric oxide synthesis; (2) antiallergic effects through blocking mast cell-mediated histamine release; and (3) antioxidant effects through increased activities of catalase, superoxide dismutase, and glutathione peroxidase in the liver with enhanced radical scavenging and reducing activity.^{130–132}

Sesquiterpene lactone and xanthatin, specific components of *Xanthium sibiricum*, displayed significant antibacterial activity against methicillin-resistant *Staphylococcus aureus* while also inhibiting other bacteria like *Staphylococcus epidermidis*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Pseudomonas aeruginosa*, and *Salmonella typhi*.¹³³

Zhao and colleagues^{134,135} found that *Xanthii fructus* was able to modulate proinflammatory cytokines through inhibition of human mast cells and peripheral blood mononuclear cells and demonstrated that Shi-Bi-Lin, a modified version of the Chinese herbal formula Cang Er Zi San, ameliorated nasal symptoms, such as sneezing and nasal scratching, in a guinea pig model through reduced nasal thromboxane B₂, eosinophil infiltration, and endothelial nitric oxide synthase activity. A double-blind, RCT enrolling 126 patients with allergic rhinitis with equal cohorts receiving Shi-Bi-Lin and placebo found that Shi-Bi-Lin significantly improved symptoms with a sustained response for at least 2 weeks after treatment.¹³⁶

However, caution must be exercised when using either *Xanthii fructus* or Cang Er Zi Wan because they have been shown to lead to certain side effects like muscle spasm and hepatotoxicity and nephrotoxicity.^{137,138}

***Flos magnoliae* (Chinese herbal name: Xin Yi Hua)**

The primary bioactive components of *Flos magnoliae* include terpenoids, lignans, neolignans, epimagnolin, and fargesin.¹³⁹ Neolignans have been found to have antiinflammatory effects through mechanisms of action different from steroids, while epimagnolin and fargesin decrease production of nitric oxide, a potent mediator in inflammation, through inhibition of inducible nitric oxide synthase expression.^{140,141} *Flos magnoliae* also demonstrates antiallergy activity via inhibition of immediate-type hypersensitivity reactions through blocking mast cell degranulation.¹⁴² As an essential oil, its main chemical ingredients have been identified as 1,8-cineole, sabinene, beta-pinene, alpha-pinene, and transcaryophyllene.⁷⁶

Chinese herbal supplements (postoperative)

Bi Yuan Shu is a Chinese herbal liquid mixture comprised of an unknown number of herbs but is reported to include at least *Magnolia liliflora*, *Xanthium strumarium*, *Astragalus membranaceus*, *Angelica dahurica*, and *Scutellaria baicalensis*. A multicenter RCT divided 340 postoperative patients with chronic RS and nasal polyps who had undergone endoscopic sinus surgery into 2 groups, with both groups receiving antibiotics and topical steroids; the test group was also treated with Bi Yuan Shu (10 mL 3 times per day).¹⁴³ Adjunctive treatment with Bi Yuan Shu was found to have significantly higher response rates on days 7, 14, 30, and 60 for purulent nasal discharge, breathing difficulty, pain, hyposmia, and halitosis, with positive trends noted for fever and cough.⁷¹

Table 1		
Acupuncture point locations and indications		
Name	Location	Purpose
Sinus Specific		
LI-4 (He Gu)	On the dorsum of the hand, at the midpoint of the second metacarpal bone, near its radial border	Nasal congestion, rhinorrhea, headache, wind-cold TCM pattern, neck pain, facial pain, stress
GB-20 (Feng Chi)	Near the base of skull, in the depression between the origins of the sternocleidomastoid and trapezius muscles	Nasal congestion, rhinorrhea, headache, wind-cold TCM pattern
ST-3 (Ju Liao)	Lateral to the nasolabial groove, level with the lower border of the ala nasi, directly inferior to the midpoint of the eye	Pain and swelling involving the maxillary sinus
LI-20 (Ying Xiang)	In the nasolabial groove, at the level of the midpoint of the lateral border of the ala nasi	Nasal congestion, rhinorrhea, anosmia
UB-2 (Zan Zhu)	Superior to the inner canthus, in a depression at the medial border of the eyebrow	Rhinitis, pain and swelling of the frontal sinus, frontal headache, wind TCM pattern
DU-23 (Shang Xing)	At the top of the head on the midline, 1 finger breadth posterior to the anterior hairline	Nasal obstruction and discharge, headache, rhinitis
Quality-of-Life Improvement		
LI-11 (Qu Chi)	With the elbow flexed, at the lateral end of the transverse cubital crease	Loss of voice, sore throat, heat TCM pattern
SJ-5 (Wai Guan)	Three finger breadths proximal to the wrist crease, on the radial side of the extensor digitorum communis tendons	Headache, neck pain, wind-heat TCM pattern
GB-21 (Jian Jing)	Midway between the spinous process of C7 and the tip of the acromion, at the highest point of the trapezius muscle	Neck pain, cough, phlegm
P-6 (Nei Guan)	Three finger breadths proximal to the wrist crease in between the tendons of the palmaris longus and flexor carpi radialis	Anxiety, pain of the head and neck, cough
ST-36 (Zu San Li)	With the knee extended, 4 finger breadths below the patella, just lateral to the tibia within the tibialis anterior muscle	Fatigue, vitality
LIV-3 (Tai Chong)	On the dorsum of the foot, in the depression distal to the junction of the first and second metatarsal bones	Headache, insomnia, stress, irritability

From Suh JD, Wu AW, Taw MB, et al. Treatment of recalcitrant chronic rhinosinusitis with integrative east-west medicine: a pilot study. *Arch Otolaryngol Head Neck Surg* 2012;138(3):294–300, with permission; and *Data from* Deadman P, Al-Khafaji M, Baker K. *A manual of acupuncture*. 2nd edition. Hove (England): Journal of Chinese Medicine Publications; 2001.

Another study assessing the efficacy of Chinese herbal medicine in the care of patients after undergoing endoscopic sinus surgery enrolled 97 patients into one of 3 treatment arms: (1) Tsang-Erh-San extract granules and Houltuynia extract powder, (2) oral amoxicillin, or (3) placebo. The study found no benefit of either treatment group over placebo.¹⁴⁴

MULTI-MODAL APPROACHES

A multicenter, nonrandomized study of 63 patients with acute RS comparing multiple conventional (antibiotics, secretolytics and sympathomimetics) with combination complementary (Sinupret and homeopathic remedy, Cinnabaris 3X) therapies demonstrated similar effectiveness based on patients' self-assessment score, physicians' score, and HCG-5 questionnaire.¹⁴⁵ However, the only validated outcome parameter was the HCG-5 quality-of-life instrument. Other limitations with this study included a small sample size and lack of randomization and blinding.

Recently, a pilot study at the University of California, Los Angeles was conducted using integrative East-West medicine to treat patients with recalcitrant chronic RS.¹⁴⁶ Eleven patients underwent 8 weekly sessions of sequential acupuncture (**Table 1**) and therapeutic acupressure style massage and had received education consisting of dietary modification, lifestyle changes, and self-acupressure. Four items on the SNOT-20 (need to blow nose, runny nose, reduced concentration, and frustrated/restless/irritable) and 3 of 8 domains on the SF-36 (role physical, vitality, and social functioning) showed a statistically significant difference, whereas trends of improvement were noted in most other elements on both quality-of-life instruments. Although the data looks promising, this study was also limited by its small size and lack of randomization and control group.

PATIENT SELF-TREATMENTS

Lifestyle modifications can also be conducive toward achieving optimal sinus health and function. These modifications include regular aerobic exercise, adequate hydration, steam inhalation, stress management, and good-quality sleep. Minimizing exposure to pollution, smoke, and environmental toxins as well as incorporating nutritional changes, such as consuming an antiinflammatory diet and avoiding dairy products, refined sugars, and processed foods, are important.¹⁴⁷ A regular spiritual practice, such as prayer, is also beneficial, along with anger management and attitudes of forgiveness, gratitude, and optimism.¹⁴⁸ Self-acupressure of certain acupoints can also be helpful to reduce sinus-related symptoms (see **Table 1**).

SUMMARY

As we gain a greater understanding of the complex pathogenesis of RS, what is becoming apparent is a shift in philosophic paradigm. Our previous reductionist models of disease and health are being replaced by holism, systems biology, and complex, nonlinear dynamics.^{149–151} Holism is a central philosophic underpinning of integrative medicine and many CIM modalities, such as TCM.

We now see this paradigm shift in our approach to RS. No longer is the medical community looking at the diagnosis of RS as solely an infectious process but rather as complex and multifactorial.¹⁵² For example, Palmer⁴¹ elegantly describes this transition whereby “generations of doctors and scientists were taught to envision bacteria as single cells that float or swim through some fluid ... in fact, rhinologists continue to foster this view”; however, “biofilms are not just single cells, but are structurally

and metabolically heterogeneous multicellular communities.¹⁵³ Biofilms demonstrate cell-to-cell signaling, a phenomenon known as “quorum sensing.”¹⁵⁴ Such is an example of complexity science and holism.

The therapeutic repertoire, likewise, has broadened significantly from antibiotics alone as the mainstay of treatment to the use of multiple therapies to act on different pathophysiological facets of RS. Integrative medicine provides an expanded approach and armamentarium to help patients with RS, whether acute, chronic, or recalcitrant.

Summary box: recommendations for clinicians and algorithm for CIM treatment

Dietary recommendations	<ul style="list-style-type: none"> • [6]-Gingerol: as ginger tea, soup, or food; consider as dietary supplement • Quercetin: as food (eg, apples, onions); consider as dietary supplement • EGCG: as green tea (<i>Camellia sinensis</i>); consider as dietary supplement • Horseradish: consider as a condiment to food
Medical treatments	<ul style="list-style-type: none"> • Intranasal or systemic steroids • Topical or oral antibiotics • Nasal saline irrigation • Topical or systemic decongestants • Antihistamines • Leukotriene antagonists • Mucolytics • Expectorants • Immunotherapy • Analgesics
If recalcitrant, consider	<ul style="list-style-type: none"> • Endoscopic sinus surgery • Antifungals • Proton-pump inhibitors • Bacterial lysates • Immunomodulators and immunostimulants • Long-term, low-dose macrolide therapy for antiinflammatory effects
Herbal supplements (starting with strongest evidence)	<ul style="list-style-type: none"> • <i>Pelargonium sidoides</i> EPs 7630: 60 drops 3 times daily, up to 3 weeks • Sinupret: either 2 tablets or 30 drops of liquid formula 3 times per day • Sinfrontal: 1 tablet every hour until improvement noted, after which change to 2 tablets 3 times per day (maximum of 12 tablets daily), up to 3 weeks • Bromelain: 500–2000 mg/d • Cineole: 200 mg 3 times per day (consider using during first 4 days of acute rhinosinusitis)

TCM	<ul style="list-style-type: none"> • Esberitox: 3 tablets 3 times per day • Myrtol extract: 300 mg/d • Consider cod liver oil with multivitamin containing selenium for children with recurrent, chronic rhinosinusitis • Consider topical manuka honey • Acupuncture: trial of 8 weekly sessions • Acupressure style massage • Consider Chinese herbal medicine <ul style="list-style-type: none"> ◦ <i>Xanthii fructus</i> (Chinese name: Cang Er Zi) ◦ <i>Flos magnoliae</i> (Chinese herbal name: Xin Yi Hua) • Postoperative (status-post endoscopic sinus surgery) <ul style="list-style-type: none"> ◦ Consider Bi Yuan Shu (10 mL 3 times per day) as adjunctive therapy
Lifestyle recommendations	<ul style="list-style-type: none"> • Minimize exposure to pollution, smoke, and environmental toxins • Adequate hydration • Steam inhalation • Avoidance of dairy products, refined sugars, and processed foods • Regular aerobic exercise • Stress management • Good-quality sleep • Regular spiritual practice, such as prayer • Expressing gratitude, forgiveness, and optimism • Anger management • Self-acupressure

REFERENCES

1. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. *Otolaryngol Head Neck Surg* 1997;117(3 Pt 2):S1–7.
2. Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis [review]. *Otolaryngol Head Neck Surg* 2007;137(Suppl 3):S32–45.
3. Pleis JR, Lucas JW, Ward BW. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. *Vital Health Stat* 10 2009;(242):1–157.
4. Cherry DK, Hing E, Woodwell DA, et al. National Ambulatory Medical Care Survey: 2006 summary. National Center for Health Statistics. *Natl Health Stat Report* 2008;(3):1–29.
5. Cullen KA, Hall MJ, Golosinskiy A. Ambulatory surgery in the United States, 2006. National Health Statistics Report. *Vital Health Stat* 2009;(11):1–28.

6. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg* 1995;113(1):104–9.
7. Senior BA, Glaze C, Benninger MS. Use of the Rhinosinusitis Disability Index (RSDI) in rhinologic disease. *Am J Rhinol* 2001;15(1):15–20.
8. Bhattacharyya N. Incremental health care utilization and expenditures for chronic rhinosinusitis in the United States. *Ann Otol Rhinol Laryngol* 2011;120(7):423–7.
9. Anand VK. Epidemiology and economic impact of rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl* 2004;193:3–5.
10. Anon JB, Jacobs MR, Poole MD, et al. Sinus and Allergy Health Partnership (SAHP). Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2004;130(Suppl 1):1–45.
11. Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al. Antibiotics for acute maxillary sinusitis. *Cochrane Database Syst Rev* 2008;(2):CD000243.
12. Small CB, Bachert C, Lund VJ, et al. Judicious antibiotic use and intranasal corticosteroids in acute rhinosinusitis. *Am J Med* 2007;120(4):289–94.
13. Piomchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. *Cochrane Database Syst Rev* 2011;(5):CD008233.
14. Ip S, Fu L, Balk E, et al. Update on acute bacterial rhinosinusitis. Evidence report/technology assessment No. 124. AHRQ Publication No. 05-E020-2. Rockville (MD): Agency for Healthcare Research and Quality; 2005.
15. Poole MD. Acute bacterial rhinosinusitis: clinical impact of resistance and susceptibility. *Am J Med* 2004;117(Suppl 3A):29S–38S.
16. Kunin CM. Resistance to antimicrobial drugs—a worldwide calamity. *Ann Intern Med* 1993;118(7):557–61.
17. Smith TL, Litvack JR, Hwang PH, et al. Determinants of outcomes of sinus surgery: a multi-institutional prospective cohort study. *Otolaryngol Head Neck Surg* 2010;142(1):55–63.
18. Brandsted R, Sindwani R. Impact of depression on disease-specific symptoms and quality of life in patients with chronic rhinosinusitis. *Am J Rhinol* 2007;21(1):50–4.
19. Davis GE, Yueh B, Walker E, et al. Psychiatric distress amplifies symptoms after surgery for chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 2005;132(2):189–96.
20. Bhattacharyya N. Clinical and symptom criteria for the accurate diagnosis of chronic rhinosinusitis. *Laryngoscope* 2006;116(7 Pt 2 Suppl 110):1–22.
21. Eisenberg DM, Davis RB, Ettner S, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA* 1998;280(18):1569–75.
22. Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. *N Engl J Med* 1993;328(4):246–52.
23. Tindle HA, Davis RB, Phillips RS, et al. Trends in use of complementary and alternative medicine by US adults: 1997-2002. *Altern Ther Health Med* 2005;11(1):42–9.
24. Barnes PM, Powell-Griner E. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data. Vital Health Stat* 2004;(343):1–19.
25. Krouse JH, Krouse HJ. Patient use of traditional and complementary therapies in treating rhinosinusitis before consulting an otolaryngologist. *Laryngoscope* 1999;109(8):1223–7.

26. Asher BF, Seidman M, Snyderman C. Complementary and alternative medicine in otolaryngology. *Laryngoscope* 2001;111(8):1383–9.
27. Pletcher SD, Goldberg AN, Lee J, et al. Use of acupuncture in the treatment of sinus and nasal symptoms: results of a practitioner survey. *Am J Rhinol* 2006; 20(2):235–7.
28. Blanc PD, Trupin L, Earnest G, et al. Alternative therapies among adults with a reported diagnosis of asthma or rhinosinusitis: data from a population-based survey. *Chest* 2001;120(5):1461–7.
29. Rotenberg BW, Bertens KA. Use of complementary and alternative medical therapies for chronic rhinosinusitis: a Canadian perspective. *J Otolaryngol Head Neck Surg* 2010;39(5):586–93.
30. Newton JR, Santangeli L, Shakeel M, et al. Use of complementary and alternative medicine by patients attending a rhinology outpatient clinic. *Am J Rhinol Allergy* 2009;23(1):59–63.
31. Yakirevitch A, Bedrin L, Migirov L, et al. Use of alternative medicine in Israeli chronic rhinosinusitis patients. *J Otolaryngol Head Neck Surg* 2009;38(4):517–20.
32. Report of the Rhinosinusitis Task Force Committee Meeting. Alexandria, Virginia, August 17, 1996. *Otolaryngol Head Neck Surg* 1997;117(3 Pt 2):S1–68.
33. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 2007;(20):1–136.
34. Benninger MS, Ferguson BJ, Hadley JA, et al. Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology and pathophysiology. *Otolaryngol Head Neck Surg* 2003;129(Suppl 3):S1–32.
35. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: establishing definitions for clinical research and patient care. *Otolaryngol Head Neck Surg* 2004; 131(Suppl 6):S1–62.
36. Hilding AC. The role of the respiratory mucosa in health and disease. *Minn Med* 1967;50(6):915–9.
37. Loehrl TA. Autonomic function and dysfunction of the nose and sinuses. *Otolaryngol Clin North Am* 2005;38(6):1155–61.
38. Grossan M. The saccharin test of nasal mucociliary function. *Eye Ear Nose Throat Mon* 1975;54(11):415–7.
39. Kennedy DW. Pathogenesis of chronic rhinosinusitis. *Ann Otol Rhinol Laryngol Suppl* 2004;193:6–9.
40. Van Crombruggen K, Zhang N, Gevaert P, et al. Pathogenesis of chronic rhinosinusitis: inflammation. *J Allergy Clin Immunol* 2011;128(4):728–32.
41. Palmer JN. Bacterial biofilms: do they play a role in chronic sinusitis? *Otolaryngol Clin North Am* 2005;38(6):1193–201, viii.
42. Ponikau JU, Sherris DA, Kern EB, et al. The diagnosis and incidence of allergic fungal sinusitis. *Mayo Clin Proc* 1999;74(9):877–84.
43. Luong A, Marple B. The role of fungi in chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005;38(6):1203–13.
44. Chiu AG. Osteitis in chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005; 38(6):1237–42.
45. Seiberling KA, Grammer L, Kern RC. Chronic rhinosinusitis and superantigens. *Otolaryngol Clin North Am* 2005;38(6):1215–36, ix.
46. Bachert C, Gevaert P, Holtappels G, et al. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol* 2001;107(4): 607–14.
47. Ferguson BJ, Otto BA, Pant H. When surgery, antibiotics, and steroids fail to resolve chronic rhinosinusitis. *Immunol Allergy Clin North Am* 2009;29(4):719–32.

48. Lacroix JS, Ricchetti A, Lew D, et al. Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. *Acta Otolaryngol* 2002;122(2):192–6.
49. Desrosiers MY, Kilty SJ. Treatment alternatives for chronic rhinosinusitis persisting after ESS: what to do when antibiotics, steroids and surgery fail. *Rhinology* 2008;46(1):3–14.
50. Lund VJ. Maximal medical therapy for chronic rhinosinusitis. *Otolaryngol Clin North Am* 2005;38(6):1301–10, x.
51. Statham MM, Seiden A. Potential new avenues of treatment for chronic rhinosinusitis: an anti-inflammatory approach. *Otolaryngol Clin North Am* 2005;38(6):1351–65, xi.
52. Woodbury K, Ferguson BJ. Recalcitrant chronic rhinosinusitis: investigation and management. *Curr Opin Otolaryngol Head Neck Surg* 2011;19(1):1–5.
53. Suzuki H, Ikeda K. Mode of action of long-term low-dose macrolide therapy for chronic sinusitis in the light of neutrophil recruitment. *Curr Drug Targets Inflamm Allergy* 2002;1(1):117–26.
54. Cervin A, Wallwork B. Macrolide therapy of chronic rhinosinusitis. *Rhinology* 2007;45(4):259–67.
55. Tamaoki J, Kadota J, Takizawa. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med* 2004;117(Suppl 9A):5S–11S.
56. Smith TL, Batra PS, Seiden AM, et al. Evidence supporting endoscopic sinus surgery in the management of adult chronic rhinosinusitis: a systematic review. *Am J Rhinol* 2005;19(6):537–43.
57. Bladt S, Wagner H. From the Zulu medicine to the European phytomedicine Umckaloabo. *Phytomedicine* 2007;14(Suppl 6):2.
58. Kolodziej H. Fascinating metabolic pools of *Pelargonium sidoides* and *Pelargonium reniforme*, traditional and phytomedicinal sources of the herbal medicine Umckaloabo. *Phytomedicine* 2007;14(Suppl 6):9–17.
59. Janecki A, Kolodziej H. Anti-adhesive activities of flavan-3-ols and proanthocyanidins in the interaction of group A-streptococci and human epithelial cells. *Molecules* 2010;15(10):7139–52.
60. Kolodziej H, Kayser O, Radtke OA, et al. Pharmacological profile of extracts of *Pelargonium sidoides* and their constituents. *Phytomedicine* 2003;10(Suppl 4):18–24.
61. Michaelis M, Doerr HW, Cinatl J Jr. Investigation of the influence of EPs® 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses. *Phytomedicine* 2011;18(5):384–6.
62. Kayser O, Kolodziej H, Kiderlen AF. Immunomodulatory principles of *Pelargonium sidoides*. *Phytother Res* 2001;15(2):122–6.
63. Conrad A, Hansmann C, Engels I, et al. Extract of *Pelargonium sidoides* (EPs 7630) improves phagocytosis, oxidative burst, and intracellular killing of human peripheral blood phagocytes in vitro. *Phytomedicine* 2007;14(Suppl 6):46–51.
64. Janecki A, Conrad A, Engels I, et al. Evaluation of an aqueous-ethanolic extract from *Pelargonium sidoides* (EPs® 7630) for its activity against group A-streptococci adhesion to human HEp-2 epithelial cells. *J Ethnopharmacol* 2011;133(1):147–52.
65. Bachert C, Schapowal A, Funk P, et al. Treatment of acute rhinosinusitis with the preparation from *Pelargonium sidoides* EPs 7630: a randomized, double-blind, placebo-controlled trial. *Rhinology* 2009;47(1):51–8.
66. Timmer A, Günther J, Rücker G, et al. *Pelargonium sidoides* extract for acute respiratory tract infections. *Cochrane Database Syst Rev* 2008;(3):CD006323.

67. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci* 2001;58(9):1234–45.
68. Seltzer AP. Adjunctive use of bromelains in sinusitis: a controlled study. *Eye Ear Nose Throat Mon* 1967;46(10):1281–8.
69. Ryan RE. A double-blind clinical evaluation of bromelains in the treatment of acute sinusitis. *Headache* 1967;7(1):13–7.
70. Taub SJ. The use of bromelains in sinusitis: a double-blind clinical evaluation. *Eye Ear Nose Throat Mon* 1967;46(3):361–2.
71. Guo R, Canter PH, Ernst E. Herbal medicines for the treatment of rhinosinusitis: a systematic review. *Otolaryngol Head Neck Surg* 2006;135(4):496–506.
72. Braun JM, Schneider B, Beuth HJ. Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme bromelain-POS in children with acute sinusitis in Germany. *In Vivo* 2005;19(2):417–21.
73. Schulz V, Hänsel R, Blumenthal M, et al. *Rational phytotherapy: a physicians' guide to herbal medicine*. 5th edition. Heidelberg (Germany): Springer; 2004.
74. Hidaka M, Nagata M, Kawano Y, et al. Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. *Biosci Biotechnol Biochem* 2008;72(2):406–11.
75. Kelly GS. Bromelain: a literature review and discussion of its therapeutic applications. *Alt Med Rev* 1996;1(4):243–57.
76. Wu W. GC-MS analysis of chemical components in essential oil from *Flos magnoliae*. *Zhong Yao Cai* 2000;23(9):538–41 [in Chinese].
77. Dorow P, Weiss T, Felix R, et al. Effect of a secretolytic and a combination of pinene, limonene and cineole on mucociliary clearance in patients with chronic obstructive pulmonary disease. *Arzneimittelforschung* 1987;37(12):1378–81 [in German].
78. Juergens UR, Engelen T, Racké K, et al. Inhibitory activity of 1,8-cineol (eucalyptol) on cytokine production in cultured human lymphocytes and monocytes. *Pulm Pharmacol Ther* 2004;17(5):281–7.
79. Santos FA, Rao VS. Antiinflammatory and antinociceptive effects of 1,8-cineole a terpenoid oxide present in many plant essential oils. *Phytother Res* 2000;14(4):240–4.
80. Kehrl W, Sonnemann U, Dethlefsen U. Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial. *Laryngoscope* 2004;114(4):738–42.
81. Tesche S, Metternich F, Sonnemann U, et al. The value of herbal medicines in the treatment of acute non-purulent rhinosinusitis. Results of a double-blind, randomised, controlled trial. *Eur Arch Otorhinolaryngol* 2008;265(11):1355–9.
82. Rajakumar K. Vitamin D, cod-liver oil, sunlight, and rickets: a historical perspective. *Pediatrics* 2003;112(2):e132–5.
83. Karkos PD, Leong SC, Arya AK, et al. 'Complementary ENT': a systematic review of commonly used supplements. *J Laryngol Otol* 2007;121(8):779–82.
84. Linday LA, Dolitsky JN, Shindledecker RD. Nutritional supplements as adjunctive therapy for children with chronic/recurrent sinusitis: pilot research. *Int J Pediatr Otorhinolaryngol* 2004;68(6):785–93.
85. Irish J, Blair S, Carter DA. The antibacterial activity of honey derived from Australian flora. *PLoS One* 2011;6(3):e18229.
86. Kwakman PH, Zaat SA. Antibacterial components of honey. *IUBMB Life* 2012;64(1):48–55. <http://dx.doi.org/10.1002/iub.578>.
87. Alandejani T, Marsan J, Ferris W, et al. Effectiveness of honey on *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms. *Otolaryngol Head Neck Surg* 2009;141(1):114–8.

88. Jarvis-Bardy J, Foreman A, Bray S, et al. Methylglyoxal-infused honey mimics the anti-Staphylococcus aureus biofilm activity of manuka honey: potential implication in chronic rhinosinusitis. *Laryngoscope* 2011;121(5):1104–7.
89. Thamboo A, Thamboo A, Philpott C, et al. Single-blind study of manuka honey in allergic fungal rhinosinusitis. *J Otolaryngol Head Neck Surg* 2011;40(3):238–43.
90. Glatthaar-Saalmüller B, Rauchhaus U, Rode S, et al. Antiviral activity in vitro of two preparations of the herbal medicinal product Sinupret against viruses causing respiratory infections. *Phytomedicine* 2011;19(1):1–7.
91. Virgin F, Zhang S, Schuster D, et al. The bioflavonoid compound, Sinupret, stimulates transepithelial chloride transport in vitro and in vivo. *Laryngoscope* 2010;120(5):1051–6.
92. Richstein A, Mann W. Treatment of chronic sinusitis with Sinupret. *Therapie der Gegenwart* 1980;119(9):1055–60 [in German].
93. Neubauer N, März RW. Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis. *Phytomedicine* 1994;1:177–81.
94. Zimmer M. Gezielte konservative Therapie der akuten Sinusitis in der HNO-Praxis. *Therapiewoche* 1985;35:4042–408.
95. Reden J, El-Hifnawi DJ, Zahnert T, et al. The effect of a herbal combination of primrose, gentian root, vervain, elder flowers, and sorrel on olfactory function in patients with a sinonasal olfactory dysfunction. *Rhinology* 2011;49(3):342–6.
96. Wüstenberg P, Henneicke-von Zepelin HH, Köhler G, et al. Efficacy and mode of action of an immunomodulator herbal preparation containing Echinacea, wild indigo, and white cedar. *Adv Ther* 1999;16(1):51–70.
97. Naser B, Lund B, Henneicke-von Zepelin HH, et al. A randomized, double-blind, placebo-controlled, clinical dose-response trial of an extract of Baptisia, Echinacea and Thuja for the treatment of patients with common cold. *Phytomedicine* 2005;12(10):715–22.
98. Beuscher N, Kietzmann M, Bien E, et al. Interference of myrtol standardized with inflammatory and allergic mediators. *Arzneimittelforschung* 1998;48(10):985–9.
99. Federspil P, Wulkow R, Zimmermann T. Effects of standardized Myrtol in therapy of acute sinusitis—results of a double-blind, randomized multicenter study compared with placebo. *Laryngorhinootologie* 1997;76(1):23–7 [in German].
100. Conrad A, Kolberg T, Engels I, et al. In vitro study to evaluate the antibacterial activity of a combination of the haulm of nasturtium (*Tropaeoli majoris herba*) and of the roots of horseradish (*Armoraciae rusticanae radix*). *Arzneimittelforschung* 2006;56(12):842–9 [in German].
101. Goos KH, Albrecht U, Schneider B. On-going investigations on efficacy and safety profile of a herbal drug containing nasturtium herb and horseradish root in acute sinusitis, acute bronchitis and acute urinary tract infection in children in comparison with other antibiotic treatments. *Arzneimittelforschung* 2007;57(4):238–46 [in German].
102. Dugasani S, Pichika MR, Nadarajah VD, et al. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. *J Ethnopharmacol* 2010;127(2):515–20.
103. Chirumbolo S. The role of quercetin, flavonols and flavones in modulating inflammatory cell function. *Inflamm Allergy Drug Targets* 2010;9(4):263–85.
104. Xiao X, Shi D, Liu L, et al. Quercetin suppresses cyclooxygenase-2 expression and angiogenesis through inactivation of P300 signaling. *PLoS One* 2011;6(8):e22934.

105. Park HH, Lee S, Son HY, et al. Flavonoids inhibit histamine release and expression of proinflammatory cytokines in mast cells. *Arch Pharm Res* 2008;31(10):1303–11.
106. Zhang S, Smith N, Schuster D, et al. Quercetin increases cystic fibrosis transmembrane conductance regulator-mediated chloride transport and ciliary beat frequency: therapeutic implications for chronic rhinosinusitis. *Am J Rhinol Allergy* 2011;25(5):307–12.
107. Maeda-Yamamoto M, Ema K, Shibuichi I. In vitro and in vivo anti-allergic effects of 'benifuuki' green tea containing O-methylated catechin and ginger extract enhancement. *Cytotechnology* 2007;55(2–3):135–42.
108. Chang JH, Song KJ, Kim HJ, et al. Dietary polyphenols affect MUC5AC expression and ciliary movement in respiratory cells and nasal mucosa. *Am J Rhinol Allergy* 2010;24(2):e59–62.
109. Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. *Ann Intern Med* 2003;138(5):393–9.
110. Witt CM, Lüdtke R, Willich SN. Homeopathic treatment of patients with chronic sinusitis: a prospective observational study with 8 years follow-up. *BMC Ear Nose Throat Disord* 2009;9:7.
111. Zabolotnyi DI, Kneis KC, Richardson A, et al. Efficacy of a complex homeopathic medication (Sinfrontal) in patients with acute maxillary sinusitis: a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial. *Explore* 2007;3(2):98–109.
112. Kneis KC, Gandjour A. Economic evaluation of Sinfrontal in the treatment of acute maxillary sinusitis in adults. *Appl Health Econ Health Policy* 2009;7(3):181–91.
113. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med* 2002;136(5):374–83.
114. Yap L, Pothula VB, Warner J, et al. The root and development of otorhinolaryngology in traditional Chinese medicine. *Eur Arch Otorhinolaryngol* 2009;266:1353–9.
115. Cabioglu MT, Cetin BE. Acupuncture and immunomodulation. *Am J Chin Med* 2008;36(1):25–36.
116. Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, et al. Anti-inflammatory actions of acupuncture. *Mediators Inflamm* 2003;12(2):59–69.
117. Carpenter RJ, Dillard J, Zion AS, et al. The acute effects of acupuncture upon autonomic balance in healthy subjects. *Am J Chin Med* 2010;38(5):839–47.
118. Zhou W, Longhurst JC. Neuroendocrine mechanisms of acupuncture in the treatment of hypertension. *Evid Based Complement Alternat Med* 2012;2012:878673.
119. Hui KK, Marina O, Liu J, et al. Acupuncture, the limbic system, and the anticorrelated networks of the brain. *Auton Neurosci* 2010;157(1–2):81–90.
120. Zhao ZQ. Neural mechanism underlying acupuncture analgesia. *Prog Neurobiol* 2008;85(4):355–7.
121. Tai S, Wang J, Sun F, et al. Effect of needle puncture and electro-acupuncture on mucociliary clearance in anesthetized quails. *BMC Complement Altern Med* 2006;6:4.
122. Sertel S, Bergmann Z, Ratzlaff K, et al. Acupuncture for nasal congestion: a prospective, randomized, double-blind, placebo-controlled clinical pilot study. *Am J Rhinol Allergy* 2009;23(6):e23–8.
123. Lundeborg T, Laurell G, Thomas M. Effect of acupuncture on sinus pain and experimentally induced pain. *Ear Nose Throat J* 1988;67(8):565–6, 571–2, 574–5.

124. Pothman R, Yeh HL. The effects of treatment with antibiotics, laser and acupuncture upon chronic maxillary sinusitis in children. *Am J Chin Med* 1982;10(1–4): 55–8.
125. Stavem K, Røssberg E, Larsson PG. Health-related quality of life in a trial of acupuncture, sham acupuncture and conventional treatment for chronic sinusitis. *BMC Res Notes* 2008;1:37.
126. Røssberg E, Larsson PG, Birkeflet O, et al. Comparison of traditional Chinese acupuncture, minimal acupuncture at non-acupoints and conventional treatment for chronic sinusitis. *Complement Ther Med* 2005;13(1):4–10.
127. Bensky D, Gamble A. Chinese herbal medicine: *Materia Medica*. Revised edition. Seattle (WA): Eastland Press; 1993.
128. Bensky D, Barolet R. Chinese herbal medicine: formulas & strategies. Seattle (WA): Eastland Press; 1990.
129. Haller CA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000;343(25):1833–8.
130. An HJ, Jeong HJ, Lee EH, et al. Xanthii fructus inhibits inflammatory responses in LPS-stimulated mouse peritoneal macrophages. *Inflammation* 2004;28(5): 263–70.
131. Hong SH, Jeong HJ, Kim HM. Inhibitory effects of Xanthii fructus extract on mast cell-mediated allergic reaction in murine model. *J Ethnopharmacol* 2003; 88(2–3):229–34.
132. Huang MH, Wang BS, Chiu CS, et al. Antioxidant, antinociceptive, and anti-inflammatory activities of Xanthii Fructus extract. *J Ethnopharmacol* 2011; 135(2):545–52.
133. Sato Y, Oketani H, Yamada T, et al. A xanthanolide with potent antibacterial activity against methicillin-resistant *Staphylococcus aureus*. *J Pharm Pharmacol* 1997;49(10):1042–4.
134. Zhao Y, Yang H, Zheng YB, et al. The effects of Fructus Xanthii extract on cytokine release from human mast cell line (HMC-1) and peripheral blood mononuclear cells. *Immunopharmacol Immunotoxicol* 2008;30(3):543–52.
135. Zhao Y, van Hasselt CA, Woo JK, et al. Effect of a Chinese herbal formula, Shi-Bi-Lin, on an experimental model of allergic rhinitis. *Ann Allergy Asthma Immunol* 2006;96(6):844–50.
136. Zhao Y, Woo KS, Ma KH, et al. Treatment of perennial allergic rhinitis using Shi-Bi-Lin, a Chinese herbal formula. *J Ethnopharmacol* 2009;122(1):100–5.
137. West PL, Mckeown NJ, Hendrickson RG. Muscle spasm associated with therapeutic use of Cang Er Zi Wan. *Clin Toxicol (Phila)* 2010;48(4):380–4.
138. Zhang XM, Zhang ZH. The study of intoxication and toxicity of Fructus Xanthii. *Zhong Xi Yi Jie He Xue Bao* 2003;1(1):71–3 [in Chinese].
139. Shen Y, Li CG, Zhou SF, et al. Chemistry and bioactivity of Flos Magnoliae, a Chinese herb for rhinitis and sinusitis. *Curr Med Chem* 2008;15(16): 1616–27.
140. Baek JA, Lee YD, Lee CB, et al. Extracts of Magnoliae flos inhibit inducible nitric oxide synthase via ERK in human respiratory epithelial cells. *Nitric Oxide* 2009; 20(2):122–8.
141. Kimura M, Suzuki J, Yamada T, et al. Anti-inflammatory effect of neolignans newly isolated from the crude drug “Shin-i” (Flos magnoliae). *Planta Med* 1985;51(4):291–3.
142. Kim HM, Yi JM, Lim KS. Magnoliae flos inhibits mast cell-dependent immediate-type allergic reactions. *Pharmacol Res* 1999;39(2):107–11.

143. Liang CY, Wen P, Zhen Y, et al. Multi-centre randomized controlled trial of bi yuan shu liquid on patients with chronic nasal sinusitis or nasal polyp after endoscopic sinus surgery. *Chin J Evid Based Med* 2004;6:377–81 [in Chinese].
144. Liang KL, Su YC, Tsai CC, et al. Postoperative care with Chinese herbal medicine or amoxicillin after functional endoscopic sinus surgery: a randomized, double-blind, placebo-controlled study. *Am J Rhinol Allergy* 2011;25(3):170–5.
145. Weber U, Luedtke R, Friese KH, et al. A non-randomised pilot study to compare complementary and conventional treatments of acute sinusitis. *Forsch Komplementarmed Klass Naturheilkd* 2002;9(2):99–104.
146. Suh JD, Wu AW, Taw MB, et al. Treatment of recalcitrant chronic rhinosinusitis with integrative East-West medicine: a pilot study. *Arch Otolaryngol Head Neck Surg* 2012;138(3):294–300.
147. Helms S, Miller A. Natural treatment of chronic rhinosinusitis. *Altern Med Rev* 2006;11(3):196–207.
148. Ivker RS. Chronic sinusitis. In: *Rakel: integrative medicine*. 2nd edition. Philadelphia, Pa: Saunders Elsevier; 2007:chap 19.
149. Federoff HJ, Gostin LO. Evolving from reductionism to holism: is there a future for systems medicine? *JAMA* 2009;302(9):994–6.
150. Weston AD, Hood L. Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. *J Proteome Res* 2004;3(2):179–96.
151. Goldberger AL, Peng CK, Lipsitz LA. What is physiologic complexity and how does it change with aging and disease? *Neurobiol Aging* 2002;23(1):23–6.
152. Ferguson BJ, Seiden A. Chronic rhinosinusitis: preface. *Otolaryngol Clin North Am* 2005;38(6):xiii–xv.
153. Costerton W, Veeh R, Shirtliff M, et al. The application of biofilm science to the study and control of chronic bacterial infections. *J Clin Invest* 2003;112(10):1466–77.
154. Platt TG, Fuqua C. What's in a name? The semantics of quorum sensing. *Trends Microbiol* 2010;18(9):383–7.