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VIRAL UPPER RESPIRATORY INFECTION

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Humanity's most frequent illness, the common cold, is caused by acute viral infection of the upper respiratory tract.¹⁻⁴ Acute respiratory infections (ARIs) are often classified as being caused either by influenza, the most serious of the common viruses, or other viruses (noninfluenza ARI). In the United States, noninfluenza ARI accounts for more than 20 million clinic visits and 40 million lost days of school and work, with total costs estimated at \$40 billion, making noninfluenza ARI the seventh most expensive illness.⁵⁻⁷ Influenza causes an annual mid-winter epidemic that varies year to year, but can be a major cause of hospitalization and death.⁸⁻¹⁰

Although colds are often considered a nuisance rather than a major public health threat, even rhinovirus, the least pathogenic of the common cold viruses, may cause death among elderly and immunocompromised individuals.¹¹⁻¹³

On average, children experience four to six symptomatic colds per year, in addition to several asymptomatic infections. For adults, the average is two to three symptomatic colds per year and perhaps one or two asymptomatic infections.¹⁴⁻¹⁶ Some individuals are particularly prone to colds, whereas others get them infrequently.¹⁷ Numerous factors appear to be involved, but overall, susceptibility remains poorly understood.

Although there still is no good proven cure for the common cold, a number of treatments have been reported to have symptom-reducing benefit in one or more randomized controlled trials (RCTs).¹⁸⁻²⁴ In terms of prevention, behavioral strategies such as hand washing, regular exercise, and smoking avoidance are widely accepted to be at least somewhat effective.²⁵⁻³¹ Immunization is considered impractical, as there are hundreds of strains of viruses. Our own research indicates training in mindfulness-based stress reduction may serve to reduce incidence, duration and impact of viral ARI.³²⁻³⁶

Pathophysiology

As an *illness*, the common cold is characterized by nasal congestion and drainage, sneezing, sore or scratchy throat, cough, and general malaise.³⁷⁻³⁹ Cough may or may not be present and tends to occur later in the disease, occasionally lasting for weeks after other symptoms have resolved. The severity of symptoms varies markedly, from barely noticeable to truly debilitating.⁴⁰ While true fever is atypical for most viruses, feelings of feverishness and chilliness are common.⁴¹

There is no proven cure for the common cold. Even the most positive previous trials have reported only modest symptomatic benefit, with little or no duration of benefit.

As an infectious *disease*, viral ARI is characterized by the replication of viruses in the nasopharyngeal epithelium,⁴² leading to a cascade of local and systemic immune responses.⁴³⁻⁴⁵ Viral replication triggers cytokine-mediated local inflammatory reactions, in addition to the recruitment of white blood cells. Parasympathetic neural pathways activate and coordinate local responses. Blood vessels dilate and capillaries leak, causing edematous tissue and transudates in the nasal passages.⁴⁶ Mucous glands are activated, resulting in mild to copious exudative discharge. Inflammatory changes in the respiratory epithelium may persist for days or weeks after viral shedding dies down. Activation of inflammatory mechanisms leading to bronchial constriction makes viral ARI the most frequent cause of asthma exacerbation.⁴⁷

Rhinovirus is the single most common etiological agent, but accounts for less than half of all ARIs.⁴⁸⁻⁵⁰ Other causative viruses include adenovirus, coronavirus, enterovirus, influenza virus, parainfluenza, and respiratory syncytial virus (RSV).^{4,51} Metapneumovirus^{52,53} and bocavirus⁵⁴⁻⁵⁶ are now known to cause ARI illness in both children and adults. There are likely additional viruses that are as yet undiscovered; even the best research laboratories fail to identify an etiological agent in up to one quarter of individuals with obvious colds. A small number of bacteria, such as streptococcus and *Haemophilus influenzae*, may cause common cold syndrome.

Respiratory viruses follow seasonal patterns. Influenza and RSV infections only occur during the winter months, with rhinovirus colds typically observed in the fall and spring. Adenovirus infection appears year-round. Parainfluenza mini-epidemics are episodic, while sporadic outbreaks of atypical agents, such as *Bordetella pertussis*, further complicate the epidemiology of ARI.

The spectrum of illness varies greatly within and among agents. In general, influenza causes the most severe illness and is therefore often classified separately from other viral ARIs. Nevertheless, the majority of illness episodes caused by influenza are indistinguishable from those caused by other viruses, with a significant number of influenza infections reported to be asymptomatic.⁵⁷⁻⁶² Less than a quarter present with the classic

“influenza-like illness” symptoms of rapid onset, fever, cough, headache, and myalgia. Despite a coordinated system to provide influenza vaccine (flu shots) each fall, influenza is implicated in as many as 20,000 deaths each year.^{8,9,63}

Psychosocial Influences

Common colds are influenced by a variety of biological, psychological, and social factors. Numerous cross-sectional and prospective epidemiological studies have provided relatively consistent findings.¹⁴⁻¹⁶ Colds occur most frequently among infants and children, and among adults in contact with them. Children who are in preschool day-care have more colds than those who are not, but have fewer colds during subsequent school years.^{64,65} While moderate regular exercise protects against infection, excess activity, such as running a marathon, increases risk temporarily.^{31,66-68} Poor mental health has been shown to be associated with increased risk.^{69,70} Stress, both acute and chronic, is known to increase ARI risk.⁷¹⁻⁷³ Sheldon Cohen first demonstrated this by showing that perceived stress predicted not only whether volunteers would become sick when exposed to rhinovirus, but whether and to what extent they would shed virus.⁷⁴⁻⁷⁶ Childhood socioeconomic status,⁷⁷ number and quality of social relationships,⁷⁸ and negative emotion^{79,80} have also been shown to predict viral shedding, as well as severity and duration of cold symptoms. Subsequent studies have corroborated these findings.^{62,71,81-84} Building on this background, my research team conducted a randomized trial finding that training people in mindfulness-based stress reduction can lead to substantive reductions in ARI illness episodes.³²⁻³⁶ An earlier study by Dr. Rakel and I on placebo effects and the influence of doctor-patient interaction indicated that empathetic patient-oriented clinicians may be able to positively influence common cold outcomes.⁸⁵

The common cold is an excellent example of how the mind and body interact. Stress can increase susceptibility while social support can reduce incidence. Perceived empathy of caregivers may also reduce illness severity and duration.

INTEGRATIVE THERAPIES

There are hundreds of reported treatments for the common cold.^{18-23,27,86} Globally, botanical remedies have been the mainstay of treatment. Descriptions of herbal therapies for common cold fill countless pages of notes and treatises by physicians, anthropologists, and ethnobotanists.⁸⁷⁻⁹⁰ However, relatively few of these traditional remedies have been adequately tested for pharmaceutical properties and clinical effectiveness. The present section will review several botanicals that are widely used or have been evaluated by randomized controlled trials (RCT). The next section will cover the use of nonbotanical complementary treatments, such as vitamin C and zinc. Finally, this chapter will briefly describe conventional

therapies, such as antihistamines, decongestants, and cough medications.

Botanicals

Andrographis (*Andrographis paniculata* or *Justicia paniculata*)

Andrographis is indigenous to Asia, with traditional use most prominent in India. Of the 28 *Andrographis* species, *A. paniculata* is most commonly used for the treatment of ARI. According to Ayurvedic tradition, Andrographis is attributed to many important medicinal properties and is used for the treatment of constipation, digestion, fever, pain, sore throat, snake bite, and to clean the blood. In the West, andrographis is most commonly used as a common cold treatment or preventative.

Various laboratories have reported antimicrobial,⁹¹ antihyperglycemic,^{92,93} antiinflammatory,⁹⁴ immunomodulatory,^{95,96} and psychopharmacological⁹⁷ effects attributable to andrographolide, flavonoids,⁹⁸ and other phytochemical constituents. There have now been at least eight RCTs published including more than 1000 subjects that have evaluated various andrographis derivatives in the treatment of ARI, including pharyngitis.⁹⁹⁻¹⁰⁶ Systematic reviews by Coon and Ernst¹⁰⁷ and Poolsup et al.¹⁰⁸ conclude the following:

*“Collectively, the data suggest that A. paniculata is superior to placebo in alleviating the subjective symptoms of uncomplicated upper respiratory tract infection. There is also preliminary evidence of a preventative effect. A. paniculata may be a safe and efficacious treatment for the relief of symptoms of uncomplicated upper respiratory tract infection; more research is warranted.”*¹⁰⁷

*“Current evidence suggests that A. paniculata extract alone or in combination with A. senticosus extract may be more effective than placebo and may be an appropriate alternative treatment of uncomplicated acute upper respiratory tract infection.”*¹⁰⁸

The most recent trial, not included in the reviews referred to previously, also reported positive results.¹⁰⁹ Based on published evidence, and with no evidence of serious safety concerns, it seems reasonable for adults to seek relief from ARI symptoms with andrographis-based cold remedies. There is insufficient evidence to favor specific products, dosing regimen, or particular standardization procedures for phytochemical content. For pregnant women and children, it seems prudent to recommend against the use of andrographis because there is little data from studies in these populations to exclude risk of harm.

DOSAGE AND STANDARDIZATION

The majority of clinical trials used products standardized to 4 or 5 mg andrographolide per tablet. A reasonable dose regimen would be two to four of these tablets, three times daily, for the first few days of a cold.

PRECAUTIONS

There are no known side effects of andrographolide; however, as with all medicinal treatments, caution and careful use are recommended.

Astragalus (*Astragalus membranaceus*; *Astragalus mongholicus*)

Astragalus is an important medicinal plant in traditional Chinese medicine.¹¹⁰ While there are dozens, if not hundreds, of reported uses, astragalus extracts are commonly used for both the treatment and prevention of the common cold.¹¹¹ While antiviral activity has been reported, immunomodulation is the purported mechanism of action. Indeed, several studies have reported the effects of astragalus on the immune system, from enhanced immunoglobulin production to restoration of lost T-cell activity.¹¹²⁻¹¹⁶ Astragalus root contains astragaloside, flavonoids, and saponins, which are variously thought to be involved in various hypothesized mechanisms of action. Unfortunately, due to a lack of human ARI trials, no clear recommendations can be made for or against the use of astragalus for the treatment or prevention of common cold, and no specific doses or precautions have been reported.

Carrageenan

Carrageenans are linear sulfated polysaccharides deriving from Irish moss (*Chondrus crispus*) and other seaweed and algae. Carrageenans are widely used in the food and cosmetics industry for the thickening, stabilizing, and gelling of a wide variety of products, including toothpaste. During the past decade, a carrageenan-based nasal spray has been tested as common cold treatment, with positive results reported.¹¹⁷ Eccles et al. reported reductions in inflammatory cytokines levels and symptoms in a randomized trial among N = 35 young adults.¹¹⁸ Fazekas et al. reported an RCT among N = 153 children, which found reductions in viral load and time to viral clearance, but no symptomatic benefit.¹¹⁹ Ludwig et al. reported an RCT among N = 211 adults, where “alleviation of symptoms was 2.1 days faster in the carrageenan group in comparison to placebo (p = 0.037).” It appears that all of these studies were sponsored by the same company, Marino Med, and that their product is available in Europe but not the United States. While these results are certainly intriguing and carrageenan nasal spray is likely safe, further research is required before specific recommendations can be made regarding its use for the treatment of URI.

DOSAGE

The formulation used in the trial above was Iota-Carrageenan (0.12%) in a saline solution, one spray in each nostril, three times daily for 4 days.

Chamomile (*Matricaria chamomilla*; *Matricaria recutita*, German chamomile; *Chamaemelum nobile*, Roman chamomile)

Chamomile has been used widely as a botanical remedy for centuries for a variety of purposes, including dysmenorrhea, gingivitis, hemorrhoids, infantile colic, indigestion, insomnia, nausea, vaginitis, and topically,

for a variety of skin conditions.¹²⁰ In the United States, chamomile is most often used as a calmate or sedative, and for the treatment of irritable bowel syndrome. However, chamomile is also used for acute respiratory infection and hence merits inclusion in the present review. As a common cold remedy, chamomile can be taken as an infusion (chamomile tea) or as an inhalation by boiling the flowering tops. A study evaluating inhaled vapors from boiling chamomile reported benefit but was of insufficient quality to reach firm conclusions.¹²¹

DOSAGE

Although there is limited evidence, a cup or two of chamomile tea as supportive treatment for the common cold is safe and may be beneficial.

PRECAUTIONS

While there are no known dose-dependent adverse reactions, allergic sensitivity, including several cases of anaphylaxis, has been reported.¹²²

Echinacea (*Echinacea angustifolia*; *Echinacea purpurea*; *Echinacea pallida*)

All dozen species from the genus *Echinacea* are indigenous to North America. Native communities discovered many medicinal uses, later transferring their knowledge to European settlers.¹²³ In the 1920s, Echinacea was introduced into Germany, where it has been popular ever since. Today, echinacea extracts are widely used in America, Europe, and elsewhere, particularly for the prevention and treatment of the common cold.¹²⁴ A considerable body of evidence exists regarding the uses of echinacea, including 24 randomized trials including more than 3000 participants,¹²⁵ and dozens of in vitro and animal studies.¹²⁶⁻¹²⁸ While there is consensus that various echinacea extracts display immunologic activities, such as promoting macrophage activation and inducing cytokine expression,¹²⁹⁻¹³⁷ there is considerable disagreement concerning which of the many echinacea-derived phytochemicals are involved. Various alkylamides, glycoproteins, polysaccharides, and caffeic, cichoric, and caftaric acids have all been implicated. Differing extracts from all three species and from various plant parts have shown immunoactivity in laboratory models. To my knowledge, no credible head-to-head, dose-finding, or viral load outcome studies have been reported, with very little pharmacokinetic information available.^{138,139} A comprehensive safety review notes a number of reported allergic reactions but suggests no dose-dependent adverse effects or major drug interaction concerns.¹⁴⁰

Randomized clinical trials testing echinacea extracts for the prevention and treatment of common cold were first conducted in Europe, with several early trials reporting positive result.¹⁴¹⁻¹⁴⁸ More recent trials in the US and elsewhere have reported mixed results, with higher quality trials finding no benefit.¹⁴⁹⁻¹⁵³ I directed two of those trials. The first was

flatly negative¹⁵⁴; however, the second observed some positive trends.¹⁵⁵ Preventive trials have all trended in beneficial directions, but none have individually demonstrated clearly positive results.¹⁵⁶ Systematic reviews of the two dozen reported trials vary in their interpretation of the evidence.¹⁵⁷⁻¹⁶³ Our recent Cochrane review¹²⁵ and JAMA publication¹⁵⁶ found no clear benefit among treatment trials but noted that prevention trials consistently favored some benefit. Not included in those reviews, a recent head-to-head trial of an echinacea tea against the antiinfluenza drug oseltamivir in influenza-like illness found the echinacea preparation to be equally effective.¹⁶⁴ A recent review argued that positive trials may be due to inadvertent unblinding, with either placebo effect or participant reporting bias contributing to false positive results.¹⁶⁵ It is also possible that negative studies have gone unreported, thereby yielding publication bias.

Given that echinacea extracts appear safe and that the vast majority of published trials have reported positive trends, it seems reasonable to cautiously support the use of echinacea in adults, particularly those with favorable personal experience and positive expectations.¹⁶⁶

DOSAGE AND STANDARDIZATION

Positive trials have used differing formulations, with preparations made from the leaf and flower of *Echinacea purpurea* most widely used. However, preliminary evidence suggests that alkylamides from the roots of *E. purpurea* and *E. angustifolia* may have the greatest bioavailability and immunoactivity.^{139,167,168} While there is a lack of consensus regarding standardization criteria, the majority of experts agree that echinacea extracts should be used as early as possible in the course of a cold, with multiple doses per day for the first few days of symptoms. Beyond that, no specific doses or precautions have been identified.

PRECAUTIONS

My own opinion is that use in children should be discouraged, as the best pediatric RCT found no positive effects but did report a slight increase in the incidence of skin rash among patients randomized to echinacea.¹⁶⁹ While there is a modest case control study finding no adverse effects in pregnancy,¹⁷⁰ I caution against its use as the risks are theoretically substantive.

There is greater evidence regarding echinacea, zinc, and vitamin C than any single conventional therapy. Unfortunately, there is a negative trial for every positive one.

Elderberry (*Sambucus nigra*)

Preliminary research indicates elderberry extracts may have antiinflammatory and antiviral antiinfluenza properties.¹⁷¹⁻¹⁷³ A Norwegian RCT among N = 60 volunteers reported potential symptom reduction benefit in influenza-like illness.¹⁷⁴ To my knowledge, those findings have not been replicated. With only one small limited trial and no good safety data, the use of elderberry for

the treatment of URI is intriguing but unlikely to become widely adopted.

Garlic (*Allium sativum*)

Garlic is widely used as a food and flavoring. Medicinally, there are hundreds of reported uses of garlic. The most prominent of these is moderation of cholesterol and other lipids, for which modest beneficial activity has been reasonably established.¹⁷⁵⁻¹⁷⁸ While in vitro studies have reported antibacterial and antiviral effects, only one relevant human trial of the efficacy of garlic in treating the common cold has been reported.¹⁷⁹ Josling reported a RCT in which 146 participants were randomized to daily garlic or placebo capsules for 12 weeks.¹⁸⁰ Dramatic between-group differences were observed, with 65 colds in the placebo group and 24 in the garlic group ($p < 0.001$), with an average cold duration of 5.0 days among those taking placebo versus 1.5 days among those taking garlic ($p < 0.05$). While the study was reportedly double-blind, proof of blinding was not provided. The active treatment was “an allicin-containing garlic supplement” dosed at “one capsule daily.” No further information on extraction methods, phytochemical composition, or amount of garlic was provided. Nevertheless, it may be reasonable to tentatively support the use of garlic as the risk of side effects is low, cardiovascular benefits are likely, and garlic is tasty.

DOSAGE

My personal recommendation is to use fresh garlic in cooking as much and often as palatable while being conscious of the cardiovascular and cold-prevention benefits of garlic.

Ginger (*Zingiber officinale*)

Ginger root is also very widely used as a food flavoring as well as for its medicinal properties. There is reasonable evidence supporting its effectiveness as an antinausea agent¹⁸¹⁻¹⁸³ and in the treatment of vertigo,¹⁸⁴ dysmenorrhea,¹⁸⁵⁻¹⁸⁷ and knee osteoarthritis.¹⁸⁸ In the ARI setting, one small trial of a ginger and goldenrod combination reported small benefits.¹⁸⁹

To my knowledge, no other trials of ginger root in the treatment of URI have been completed. Nevertheless, as ginger is widely used as a treatment for colds and flu, and as I personally happen to use ginger as a common cold remedy, it is included in this review.

DOSAGE

Buy a nice ginger root at the local grocery store, shave off the peel and slice the root thinly using a sharp knife, being careful not to cut one's fingers. Drop the sliced ginger into boiling water and steep for 5 minutes, then add honey and lemon to taste. Sip slowly, and *feel* the ginger work! (Dr. Barrett's personal recipe)

Ginseng (*Panax ginseng*, *Panax quinquefolium*)

Asian (*P. ginseng*) and American (*P. quinquefolium*) ginseng are used for a wide variety of purposes. The genus name *Panax*, chosen by Linnaeus, in fact derives from

the same root word as Panacea, the Greek goddess of healing. The most widespread medical theory supporting the use of ginseng derives from traditional Chinese medicine.¹⁹⁰ Ginseng is thought to have “adaptogenic” attributes, which bring balance, homeostasis, and healing.¹⁹¹⁻¹⁹³ Some evidence of the effectiveness of a *P. ginseng* extract in preventing common cold comes from an Italian trial among N = 227 individuals followed for 12 weeks.¹⁹⁴ A Korean preventive trial evaluating *P. ginseng* among N = 100 individuals reported 12 cases of ARI (25%) in the ginseng group, compared to 22 (45%) in the placebo group.¹⁹⁵ A series of Canadian studies of a polysaccharide-rich *P. quinquefolium* extract reported immunomodulatory changes.¹⁹⁶⁻¹⁹⁸ An RCT among N = 198 elderly nursing home residents reported reductions in both cold and flu episodes.¹⁹⁹ A second preventive trial using the same formulation among N = 323 subjects reported a statistically significant 13% difference in incidence in cold and flu episodes during 4 months of observation.^{200,201} The proprietary formula used in this series of research has been approved for use in Canada. In the U.S., it would seem reasonable for preventive-minded people to use small doses of ginseng extracts (either *P. ginseng* or *P. quinquefolium*) regularly during the cold and flu season; however, as evidence is modest and safety not established, the use of ginseng in pregnancy and among children is not advised. Evidence is insufficient to recommend specific dosing or side effects.

DOSAGE

For prevention during times of high risk, take 100 mg daily. For acute infection, consider 100 mg twice daily for 9 days.

PRECAUTIONS

Ginseng is generally well tolerated but may cause insomnia, tachycardia, and elevated blood pressure.

Goldenseal (*Hydrastis canadensis*)

Goldenseal is among the top selling botanicals in the United States. In addition to cold remedies, *Hydrastis* extracts are found in treatments for allergy and in digestive aids, feminine cleansing products, mouthwashes, shampoos, skin lotions, and laxatives.¹²⁰ Goldenseal is combined with echinacea in many cold therapies. However, there are currently no RCTs evaluating the efficacy of goldenseal, either alone or in combination with echinacea. The phytochemical constituent berberine is pharmacologically active, and in overdose can cause significant toxicity, including cardiac arrhythmia and death.²⁰² Goldenseal is contraindicated in pregnancy and lactation. Berberine-rich extracts are included in many traditional Chinese medicines. The demand for goldenseal has led to overharvesting and to the substitution of other plants containing berberine or similar compounds. Given these considerations, I do not

recommend goldenseal for the prevention or treatment of the common cold.

Lemon (*Citrus limon*)

Originally from India, the lemon tree is now cultivated throughout the world and used as a food, flavoring, and botanical remedy. Medicinal uses include the prevention and treatment of scurvy. Lemon is also used for malaria, rheumatic arthritis, and fever, in addition to numerous other indications. Lemon juice and lemon-flavored teas are used for the prevention and treatment of colds, coughs, and flu. While rigorous evidence of the effectiveness of lemon is lacking, lemon is generally recognized as safe and to have important nutritional value as a source of vitamin C (ascorbic acid), thereby making lemon a good choice for those who derive symptomatic comfort.

Peppermint (*Mentha piperita*)

Peppermint and other members of the mint family are widely used for a variety of medicinal purposes, including coughs and colds, as well as for a variety of gastrointestinal purposes. When treating colds, mint teas and infusions are taken internally, while mint oils are applied topically. Peppermint oil is composed primarily of menthol, menthone, and menthyl acetate. Menthol especially has been extracted and included in various topical cold remedies classified as “menthol rubs.” While neither mint teas nor menthol rubs have been subjected to rigorous randomized controlled trials evaluating their efficacy in treating the common cold, both applications seem reasonable from a cost, risk, and potential benefit perspective, at least in adults. More concentrated preparations, such as peppermint oil, should not be applied to the mucosa of infants or young children, as direct inflammatory toxicity can result. Bronchospasm, tongue swelling, and even respiratory arrest have been rarely reported.^{202,203}

Umckaloabo (*Pelargonium sidoides*)

Various preparations of this South African plant have been used for centuries following ethnobotanical tradition.²⁰⁴⁻²⁰⁷ Antiviral effects, including antiinfluenza activity, have been reported.^{208,209} Three RCTs in adults (N = 746) and three RCTs in children (N = 819) have yielded somewhat inconsistent yet generally positive findings.²¹⁰⁻²¹² A 2013 Cochrane review concluded that “*P. sidoides* may be effective in alleviating symptoms of acute rhinosinusitis and the common cold in adults, but doubt exists. It may be effective in relieving symptoms in acute bronchitis in adults and children, and sinusitis in adults.”²¹³ Scientific interest in *Pelargonium* is relatively recent, and conclusions to date are tentative. However, umckaloabo seems a reasonable choice for adults looking for a natural treatment for cough, cold, or bronchitis. No specific formulation or dose regimen can be recommended.

DOSAGE

The formulation used in the above research was Eps 7630, which is an 11% aqueous ethanolic extract available in Europe. In America, the most commonly available form is a 1X homeopathic dose through a variety of brand names. The effectiveness of homeopathic doses is unknown.

PRECAUTIONS

While no dose-dependent adverse effects are known, gastrointestinal disturbance and hepatotoxicity have been reported,²¹⁴ and the results of a previous study indicated that allergic reactions may be a relatively frequent problem.²¹⁵

There are several trials supporting the use of *Andrographis*, *pelargonium* (umckaloabo), and intranasal carrageenan gel. These are ones to watch!

Vitamins, Minerals, and Home Remedies**Chicken Soup**

Hot chicken soup is the epitome of traditional cold remedies, and its use is supported by many personal testimonies. Chicken soup as a cold remedy is somewhat supported by at least two human studies, one reporting inhibited neutrophil chemotaxis²¹⁶ and the other indicating increased nasal mucus velocity and decreased nasal airflow resistance.²¹⁷ No RCTs using patient-oriented outcomes have been reported. Personally, I would be much more enthusiastic if the chicken industry adopted more responsible sanitary, environmental, and animal welfare policies. In the meantime, the use of soup made from free-range chickens and substantial quantities of wholesome organic vegetables can be cautiously supported, although I personally prefer soup with vegetables only.

Honey

Honey is widely used as a food and flavoring, and has been advocated as a treatment for cough and other ARI symptoms, particularly for children. A 2012 Cochrane review found two trials including 265 children.²¹⁸⁻²²⁰ While the quality of the trials was considered mediocre, the authors concluded that “honey may be better than ‘no treatment’ and diphenhydramine in the symptomatic relief of cough but not better than dextromethorphan.”²¹⁸ These may not be fair comparators, as diphenhydramine is not known to have antitussive properties and dextromethorphan and other OTC drugs are not recommended for children.²³ Nevertheless, honey may be a reasonable choice for cough in children aged 2 to 10 years as it is safe and tastes good. Honey does contain large amount of glucose and fructose, so tooth-brushing afterwards is recommended. Honey is not recommended for infants due to the risk of *Clostridium botulinum* infection.

DOSAGE

Consider adding a teaspoon of honey to ginger, chamomile, or peppermint tea.

Consider adding a teaspoon of honey for cough and a squeeze of lemon to a tea made with one or more of the botanicals discussed as having positive evidence against viral URI.

Dry Saunas and Hot Baths

In 1990, Ernst et al. reported a nonrandomized 6-month prevention trial in which, “25 volunteers were submitted to sauna bathing, with 25 controls abstaining from this or comparable procedures. In both groups the frequency, duration and severity of common colds were recorded for 6 months. There were significantly fewer episodes of common cold in the sauna group. This was found particularly during the last 3 months of the study period when the incidence was roughly halved compared to controls. It is concluded that regular sauna bathing probably reduces the incidence of common colds, but further studies are needed to prove this.”²²¹ The research community apparently did not heed Dr. Ernst’s sage advice as, to my knowledge, there have been no subsequent trials testing the therapeutic properties of hot water bathing in the prevention or treatment of common cold. However, in 2010, Pach et al. reported a trial evaluating hot dry sauna as a treatment for the common cold, in which N = 157 individuals were randomized to wearing a winter coat in a hot dry sauna or wearing a coat in the sauna at room temperature.²²² Trends towards symptomatic benefit and reduced medication use were noted at various time points during the 7 days of treatment; however, the overall conclusion was that “inhaling hot air while in a sauna has no significant impact on overall symptom severity of the common cold.”²²² Despite the limited research on hot baths and the disappointing results of the previous dry sauna trial, these are modalities that I would personally recommend, should the opportunity exist, as long as one is reasonably healthy and the facilities are clean. However, I do not recommend wearing a winter coat in the sauna as I do not consider this proper attire. An optional bathing suit may perhaps be more appropriate, and certainly easier for laundering. There is no data regarding the optimal frequency, duration, or temperature of saunas and baths for the prevention or treatment of URI.

PRECAUTIONS

Although saunas and hot baths are generally safe and potentially therapeutic, adequate hydration and care when standing up are important because heat-induced peripheral vasodilation can lead to orthostatic hypotension, dizziness, and increased fall risk.

Inhaled Hot Moist Air

One widespread traditional cold remedy involves the inhalation of hot moist air, often with a botanical or other additive. As noted above, benefits of inhalation of vapors from chamomile tea were reported by a previous clinical trial.¹²¹ The most recent Cochrane review evaluated six heterogeneous RCTs with a total of 394 trial participants reporting mixed results.²²³ While it seems reasonable to

recommend humidification when the air is dry, and perhaps advocate the inhalation of hot moist air for those that find it comforting, it should be noted that water boils at around 100 °C, and inhalation of vapors near this temperature may cause significant thermal damage. Be careful!

Hot Toddy

I have been impressed by the number of people, including several physicians, who have come up after a lecture to tell me that their favorite cold remedy was some form of a hot alcoholic beverage, such as a “hot toddy” or hot buttered rum. While to my knowledge no trials have tested any of these remedies, testimonies of symptomatic benefit should not be totally disregarded. At a societal level, there is a well-known inverse relationship between moderate regular consumption of alcoholic beverages and the number and severity of colds.²⁸ Those who consume one or two drinks daily have fewer and less severe colds than both those who drink heavily and fewer colds than those who do not drink alcohol at all. One study found this relationship to be most pronounced for red wine.²²⁴ Personally, I like to add a bit of rum to a cup of hot orange juice as a nighttime cold remedy. However, this would be contraindicated among those with alcohol use disorders, in children, pregnant women, and individuals who need to use a motor vehicle or who operate hazardous machinery.

Nasal Saline

What could be more healthful and therapeutic than a mild saltwater rinse of the nasal cavities? While saline nasal lavage is a longstanding tradition in many cultures, it is only recently that Western biomedicine has begun to integrate this practice. Currently, there are a number of positive trials among individuals with allergic rhinitis and chronic sinus symptoms, including one at the University of Wisconsin Department of Family Medicine.²²⁵

A 2015 Cochrane review evaluated the results of five RCTs, two in adults (N = 205) and three in children (N = 544), all comparing nasal saline to routine care of common cold.²²⁶ These authors concluded, “nasal saline irrigation possibly has benefits for relieving the symptoms of acute URTIs. However, the included trials were generally too small and had a high risk of bias, reducing confidence in the evidence supporting this.” In the largest adult trial, Adam et al. randomized 140 individuals to one of three groups: hypertonic saline, normal tonic saline, or no treatment (two squirts per nostril, three times per day.) No significant differences were observed between groups in terms of duration or severity of symptoms.²²⁷ On the other hand, the largest pediatric trial published to date reported significant improvements in breathing and reductions in nasal secretions.²²⁶ In addition to trials designed to test nasal saline, there is some evidence from trials using saline as a placebo. For example, Diamond et al. reported a trial in which 955 participants were randomized to one of three doses of nasal ipratropium, to the “placebo” saline vehicle, or to no treatment at all.²²⁸ The nasal saline vehicle yielded greater benefit compared to no treatment than did any of the ipratropium doses when compared with each other or with saline.

Overall, nasal saline is a remedy with potential benefit and virtually no cost or significant risks. I suggest twice daily treatment for the first few days of a cold (see [Chapter 113](#)).

Probiotics

Probiotics are live bacteria that are thought to support healthy gastrointestinal function. Several trials have demonstrated benefit for antibiotic-associated diarrhea²²⁹ and have indicated benefit for irritable bowel syndrome and other conditions.²³⁰⁻²³⁴ Interestingly, there is now reasonably strong preliminary evidence that probiotics may also prevent or ameliorate ARI illness. This evidence includes more than a dozen trials testing the efficacy of probiotics in preventing cold and flu illness episodes.²³⁵⁻²⁴³ One RCT was conducted among elderly individuals,²⁴⁰ and two involved children.^{239,242} One of these was aimed at preventing diarrheal illness but instead provided evidence of cold and flu prevention.²⁴² Two recent meta-analyses reviewed more than a dozen RCTs including more than 3000 participants and noted “significantly fewer numbers of days of illness per person”²⁴⁴ among those receiving probiotics versus placebo, concluding that “the results implied that probiotics had a modest effect in common cold reduction.”²⁴⁵ Various formulations are available without prescription and, to my knowledge, there are no significance concerns regarding adverse effects. Until further evidence becomes available, we can be cautiously optimistic and perhaps even advocate probiotics for preventing or treating common cold; however, no specific products or dose regimens can be singled out as particularly effective (see [Chapter 105](#)).

Vitamin C (Ascorbic acid)

The use of vitamin C for the prevention and treatment of the common cold became widespread after double Nobel laureate Linus Pauling promoted his belief in this therapy in the 1950s and 1960s.²⁴⁶ By the early 1970s, three major trials conducted in Toronto by T.W. Anderson indicated preventive effectiveness.²⁴⁷⁻²⁴⁹ Over the next few decades, more than 30 trials including more than 12,000 participants have been reported.^{250,251} Interestingly, approximately half of these trials reported positive results, far more than would be expected by chance; however, this was not enough to convince more skeptical scientists. While there is no clear consensus regarding the reasons why some trials found benefit and others did not, it seems reasonable to tentatively conclude some preventive effectiveness, as concluded by a recent Cochrane systematic review:

“Regular supplementation trials have shown that vitamin C reduces the duration of colds, but this was not replicated in the few therapeutic trials that have been carried out. Nevertheless, given the consistent effect of vitamin C on the duration and severity of colds in the regular supplementation studies, and the low cost and safety, it may be worthwhile for common cold patients to test on an individual basis whether therapeutic vitamin C is beneficial for them.”²⁵⁰

The evidence supports modest preventive effectiveness for doses of 200 mg to 500 mg daily. Benefits of larger doses for prevention, or as treatment for new onset colds, is supported by some trials and systematic reviews,²⁵² while other trials have reported contradictory results.²⁵³ Given the generally accepted safety of ascorbic acid at doses up to a few grams per day over short periods, it seems reasonable to cautiously support its use in treating URI, particularly among individuals those positive experiences and expectations (very high doses, such as the 18 grams per day that Linus Pauling was reportedly taking up to his death at age 93 in 1994, have not been tested in trials and cannot be supported). Regular intake of vitamin C rich foods, however, can be enthusiastically supported because greater intake of fresh fruits and vegetables has been associated with many health benefits in dozens of large observational studies and has no known risks.

Vitamin D

In combination with calcium, vitamin D is widely recommended as a preventive or treatment for osteopenia and osteoporosis. Interest in vitamin D for a wide variety of other health concerns has blossomed over the past decade. Vitamin D for common cold prevention and treatment has been advocated, bolstered by the fact that vitamin D levels are low and ARI incidence is high during winter months.²⁵⁴ Unfortunately, enthusiasm has not been matched by evidence. To my knowledge, there is only one good quality RCT evaluating vitamin D for preventing colds.²⁵⁵ Although the results trended towards slight benefit, the general interpretation was negative.²⁵⁶

Zinc. In some ways, the story of zinc for the treatment of colds is similar to that of vitamin C. Reportedly, the physician George Eby noticed rapid recovery from an ARI in a child hospitalized and given zinc for unrelated reasons. This observation was followed by an RCT that reported positive results in 1984 (but had methodologic flaws).²⁵⁷ Since then, a dozen trials with more than 1300 participants have been conducted using various zinc preparations.²⁵⁸⁻²⁶³ Trials testing zinc acetate in doses of 75 mg or more have tended to report the most positive results.²⁶⁴ The most recent Cochrane review was generally positive,²⁵⁹ and many authorities now recommend zinc as a treatment for common cold.²⁶⁵ However, there are concerns regarding adverse effects, such as unpleasant taste and/or nausea. While zinc is an essential mineral, with many known protective effects when ingested in foods in appropriate doses,^{266,267} use of relatively high doses during acute illness may confer minimal risks. Advocates recommend frequent dosing (every 2 to 3 hours) for the first 2 or 3 days of a cold, a dosing regimen that some patients may not find convenient. Nasal irritation is common, and loss of sense of smell has been reported.²⁶⁸ My personal recommendation is to tentatively support the use of oral or nasal zinc preparations among those who have experienced benefit and/or express positive feelings about the treatment but to not recommend use among children or pregnant women.

DOSAGE

Zinc gluconate, one table or lozenge containing 9–24 mg of elemental zinc, up to every 2 or 3 hours while awake, for the first few days of ARI illness.

PRECAUTIONS

Zinc can inhibit the absorption of other minerals (copper) if used for extended periods of time. Nasal formulations have been associated with the loss of smell.

Among 13 trials of zinc including 1400 participants, approximately half reported positive and half reported negative results.

Mind Body

Placebo, Meaning, and Mind-Body Effects

During the past two decades I have read reports of hundreds of trials and dozens of systematic reviews and become increasingly convinced of the importance of mind-body effects, otherwise described as placebo or meaning effects.²⁶⁹⁻²⁷³ Positive thinking, suggestion, expectancy, and belief in the therapeutic value of a given remedy can be a powerful healing force. While regular exercise, balanced nutrition, and tobacco cessation are clearly associated with fewer and less severe illness episodes, so too are positive mental health attributes such as favorable psychological profile and healthful social relationships. Psychological predispositions, especially sociability and a positive emotional style, are predictive of both symptomatic and physiological outcomes. For the integrative clinician, this means that understanding an individual's belief system may be a crucial part of the therapeutic encounter. If a patient already believes in a safe therapy, reinforcing that belief may enhance the therapeutic response. If patients are wary of a mentioned remedy, clinicians should not press the issue. Remember that reassurance, empathy, empowerment, and positive prognosis can all be usefully employed in the clinical encounter.

Pharmaceuticals and Conventional Cold Products

Antihistamines

Drugs blocking the effects of histamine have been sold as cold remedies for more than a century but, interestingly, have been subjected to less in terms of rigorous RCT research than alternatives such as vitamin C, zinc, and echinacea. Nevertheless, there is reasonable evidence of the modest benefit of first generation antihistamines, such as diphenhydramine, clemastine fumarate, and chlorpheniramine, in reducing nasal drainage.²⁷⁴⁻²⁷⁷ However, effects appear to be more attributable to anticholinergic mechanisms than antihistamine effects, and second generation “nonsedating” antihistamines do not seem to provide benefit.²⁷⁸ For adults who do not mind

the potential sedating or membrane-drying effects, or those with allergic responses, a first generation antihistamine may be a reasonable choice. For children, where there is no positive evidence whatsoever, antihistamines should be reserved for allergic rather than infectious rhinitis.

Decongestants

The oral decongestant, pseudoephedrine, has been tested in several clinical trials and appears to have minor benefit in reducing nasal congestion and drainage.²⁷⁹⁻²⁸² Side effects, including anxiety, dizziness, insomnia, and palpitations, are fairly common. More worrisome is the potential risk of elevated blood pressure and cardiac arrhythmia. Phenylpropanolamine, for decades a popular over-the-counter decongestant, was taken off the market after studies indicated an association with increased mortality, particularly among elderly individuals.²⁸³

The topical intranasal decongestant, oxymetazoline, has been shown to decrease nasal airway resistance as well as mucus production and drainage.²⁸⁴⁻²⁸⁷ Intranasal phenylephrine has been less extensively studied but likely has similar effects. Unfortunately, these proven benefits come at the risk of nasal membrane dryness and discomfort. Oxymetazoline should be used for no more than 4 days as rebound nasal congestion can occur.

Cough Suppressants

Dextromethorphan, the active ingredient in cough remedies designated with “DM,” is widely used as an over-the-counter cough suppressant. Codeine, and to a lesser extent hydrocodone, are prescribed for cough and are thought to work through similar opioid-mediated mechanisms. As such, these medications have side effects including sedation, constipation, and, potentially, respiratory suppression. While most patients and clinicians agree that these remedies work, there is considerable debate over effect size and mechanism of action due to a lack of appropriate evidence.²⁸⁸⁻²⁹⁰ The best systematic review of cough remedies for children and adults concluded: “there is no good evidence for or against the effectiveness of OTC medicines in acute cough.”²⁹¹ Benzonatate (Tessalon perles) is licensed as a prescription antitussive but appears to have been given this indication despite a lack of good evidence.

Analgesics/Antipyretics

There is no doubt that acetaminophen and nonsteroidal antiinflammatories (NSAIDs), such as aspirin, ibuprofen, and naproxen, are effective in treating pain and fever that may accompany the common cold. However, some reports suggest that viral shedding may be prolonged by analgesics.^{292,293} While limited use for pain reduction is eminently reasonable, the widespread use of NSAIDs for general common cold symptoms is not justified, as evidence-of-benefit is marginal, and many thousands of individuals die each year from NSAID-attributable

gastrointestinal hemorrhage and congestive heart failure.²⁹⁴⁻²⁹⁶

Anticholinergics

Ipratropium nasal spray has been evaluated by several good quality RCTs regarding its efficacy in the amelioration of the symptoms of infectious and allergic rhinitis.^{297,298} These trials, including a dose-response trial among 955 individuals with community-acquired common cold,²²⁸ reported definite benefit in terms of reduced nasal congestion and drainage. Common side effects include headache, uncomfortable nasal dryness, and nosebleed.

Combination Formulas

The multibillion-dollar market in cold remedies is dominated by numerous products containing combination formulas. Loopholes in FDA regulations have allowed pharmaceutical companies to mix various decongestants, antihistamines, analgesics, and antitussives, and then market these products under a variety of brand names and questionable claims. While there is some evidence of the effectiveness of these products from several RCTs,^{274,299} very few if any of currently marketed products have been tested in large, well-controlled RCTs. Personally, I recommend against using any combination cold formula, with a possible exception for those who are convinced that a specific formula works for them. Perhaps most importantly, clinicians as well as parents should be made aware that no cold formula has ever been proven to work in children. In my opinion, acetaminophen (paracetamol) is the only currently justifiable treatment of pain in children.

Antivirals

Dozens of phase I and II trials using experimental rhinovirus infection models have reported benefit for several different antiviral drugs.³⁰⁰⁻³⁰⁴ None, however, have demonstrated safety or efficacy in the treatment of community-acquired colds and therefore none can currently be recommended. Nevertheless, this remains an active area of research; safe and effective antiviral cold treatments may become available in the future.

Conventional treatments, such as antihistamines, decongestants, and cough remedies, may help slightly with some symptoms but do tend to have side effects.

PREVENTION PRESCRIPTION

- Do not smoke
- Exercise regularly
- Wash hands frequently
- Eat a balanced nutritious diet, including foods containing vitamin C and zinc

- Maintain supportive social relationships
- Reduce exposure to people with colds
- Reduce stressors and/or negative responses to stress
- Antibiotics should not be used for the treatment of cold symptoms in children or adults.
- There is some evidence for the effectiveness of andrographis (400 mg twice daily), vitamin C (200–500 mg daily), ginseng (100 mg daily), and probiotics in the prevention of colds. As the evidence is weak, consider these treatments only during high-risk times.




There is no good evidence of the effectiveness of any treatment, conventional or integrative, in children. While children can suffer side effects, they are less likely than adults to benefit from the placebo effect. Dr. Barrett says, “Don’t drug the kids!”

THERAPEUTIC REVIEW


Below is a summary of therapeutic options for common cold. None are proven beyond reasonable doubt to be safe and effective. Nevertheless, these are all reasonable options given best current evidence of benefit and harm.



TREATMENT OF COMMON COLD

Botanicals






- Andrographis. Consistent preliminary evidence of benefit, no major concerns of harm. No good reason to pick one formulation or dose regimen over another. A common dose is 400 mg of dried herb, or extract containing 5 to 20 mg of andrographolide, up to three times daily for the first few days of illness. 
- Echinacea. Contradictory evidence, with several positive trials. Evidence on prevention is more consistent than that for treatment. No serious concerns of harm but should be avoided in pregnancy. Use three or four times daily for the first few days of a cold. No strong reason to pick one formulation over another 
- Pelargonium/Umckaloabo. Contradictory evidence, with a few positive trials. No serious concerns of harm. Use three or four times daily for the first few days of a cold. No strong reason to pick one product over another 

Supplements

- Vitamin C. Contradictory evidence, with several positive trials. Water-soluble vitamin. Necessary nutrient. Very safe in reasonable doses. 

- Zinc. Contradictory RCT evidence, with several positive trials, particularly with higher doses of zinc acetate. Use lozenges frequently for the first couple days of a cold. Side effects may include bad taste or nausea. 
- Astragalus, chamomile, garlic, ginger, ginseng, lemon, peppermint, hot baths, hot moist air, nasal saline, and chicken soup are all unproven but safe supportive therapies. 

Pharmaceuticals

- First generation (sedating) antihistamines may decrease nasal congestion but may cause drowsiness. 
- Intranasal decongestants appear to be effective in decreasing nasal congestion and drainage but quite often cause nasal dryness or irritation, and, rarely, insomnia, palpitations, or elevated blood pressure. 
- Oral decongestants may be effective in decreasing nasal congestion but may cause insomnia, palpitations, or elevated blood pressure. 
- Intranasal ipratropium appears to be effective in decreasing nasal congestion and drainage but may cause headache, nasal irritation, or nose-bleed. 
- Antivirals for true influenza of no more than 36 hours duration may reduce symptom severity, duration, and infectivity 

Key Web Resources

PubMed Health
 Medline Plus
 American Academy of Family Medicine
 Wikipedia

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0024671/>
<http://www.nlm.nih.gov/medlineplus/commoncold.html>
<http://www.aafp.org/afp/2012/0715/p153.html>
https://en.wikipedia.org/wiki/Common_cold

REFERENCES

References are available online at ExpertConsult.com.

REFERENCES

- Campbell H: Acute respiratory infection: a global challenge, *Arch Dis Child* 73(4):281–283, 1995.
- Eccles R, Weber O: *Common cold*, Basel, Switzerland, 2009, Birkhauser Verlag.
- Gwaltney JM: Rhinovirus colds: epidemiology, clinical characteristics and transmission, *Eur J Respir Dis* 128:336–339, 1983.
- Monto AS: Epidemiology of viral respiratory infections, *Am J Med* 112, 2002. Suppl-12S.
- Fendrick AM, Monto AS, Nightengale B, Sarnes M: The economic burden of non-influenza-related viral respiratory tract infection in the United States, *Arch Intern Med* 163(4):487–494, 2003.
- Palmer LA, Rousculp MD, Johnston SS, Mahadevia PJ, Nichol KL: Effect of influenza-like illness and other wintertime respiratory illnesses on worker productivity: the child and household influenza-illness and employee function (CHIEF) study, *Vaccine* 28(31):5049–5056, 2010.
- Bertino JS: Cost burden of viral respiratory infections: issues for formulary decision makers, *Am J Med* 112(Suppl 6A):42S–49S, 2002.
- Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al.: Mortality associated with influenza and respiratory syncytial virus in the United States, *JAMA* 289(2):179–186, 2003.
- Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al.: Influenza-associated hospitalizations in the United States, *JAMA* 292(11):1333–1340, 2004.
- Molinari NA, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al.: The annual impact of seasonal influenza in the US: measuring disease burden and costs, *Vaccine* 25(27):5086–5096, 2007.
- Hicks LA, Shepard CW, Britz PH, Erdman DD, Fischer M, Flannery BL, et al.: Two outbreaks of severe respiratory disease in nursing homes associated with rhinovirus, *J Am Geriatr Soc* 54(2):284–289, 2006.
- Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RT, Werno AM, et al.: Incidence and characteristics of viral community-acquired pneumonia in adults, *Thorax* 63(1):42–48, 2008.
- Louie JK, Yagi S, Nelson FA, Kiang D, Glaser CA, Rosenberg J, et al.: Rhinovirus outbreak in a long term care facility for elderly persons associated with unusually high mortality, *Clin Infect Dis* 41(2):262–265, 2005.
- Monto AS, Ullman BM: Acute respiratory illness in an American community, *JAMA* 227(2):164–169, 1974.
- Fox JP, Hall CE, Cooney MK, Luce RE, Kronmal RA: The Seattle virus watch. II. Objectives, study population and its observation, data processing and summary of illnesses, *Am J Epidemiol* 96(4):270–285, 1972.
- Gwaltney JM, Hendley JO, Simon G, Jordan Jr WS: Rhinovirus infections in an industrial population. I. The occurrence of illness, *NEJM* 275(23):1261–1268, 1966.
- Ball TM, Holberg CJ, Martinez FD, Wright AL: Is there a common cold constitution? *Ambulatory Pediatrics* 2(4):261–267, 2002.
- Allan GM, Arroll B: Prevention and treatment of the common cold: making sense of the evidence, *CMAJ* 186(3):190–199, 2014.
- Jackson AP, Simenson S: Management of common cold symptoms with over-the-counter medications: clearing the confusion, *Postgrad Med* 125(1):73–81, 2013.
- Fashner J, Ericson K, Werner S: Treatment of the common cold in children and adults, *Am Fam Physician* 86(2):153–159, 2012.
- Smith SM, Schroeder K, Fahey T: Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings, *Cochrane Database Syst Rev* 8:CD001831, 2012.
- Arroll B: Non-antibiotic treatments for upper-respiratory tract infections (common cold), *Resp Med* 99(12):1477–1484, 2005.
- Ballegeer CR, Turner RB: Supportive treatment for children with the common cold, *Curr Opin Pediatr* 26(1):114–118, 2014.
- Fahey T, Stocks N, Thomas T: Systematic review of the treatment of upper respiratory tract infection, *Arch Dis Child* 79:225–230, 1998.
- Peters EM: Exercise, immunology and upper respiratory tract infections, *Int J Sports Med* 18(1):S69–S77, 1997.
- Van Driel M, Del Mar C: Interventions to prevent transmission of the common cold. In Eccles R, Weber O, editors: *Common Cold*, Basel, Boston, Berlin, 2009, Birkhauser, pp 1–354.
- Monto AS: Epidemiology of viral respiratory infections, *Am J Med* 112(Suppl6A):4A–12A, 2002.
- Cohen S, Tyrell DAJ, Russell MAH, Jarvis MPhil MJ, Smith AP: Smoking, alcohol consumption, and susceptibility to the common cold, *Am J Public Health* 83(9):1277–1283, 1993.
- Carter JM: Hand washing decreases risk of colds and flu, *J Natl Med Assoc* 94(2):A11, 2002.
- Aiello AE, Coulborn RM, Perez V, Larson EL: Effect of hand hygiene on infectious disease risk in the community setting: a meta-analysis, *Am J Public Health* 98(8):1372–1381, 2008.
- Nieman DC, Henson DA, Austin MD, Sha W: Upper respiratory tract infection is reduced in physically fit and active adults, *Br J Sports Med*, 2010.
- Barrett B, Hayney MS, Muller D, Rakel D, Ward A, Obasi CN, et al.: Meditation or exercise for preventing acute respiratory infection: a randomized controlled trial, *Ann Fam Med* 10(4):337–346, 2012.
- Hayney MS, Coe CL, Muller D, Obasi CN, Backonja U, Ewers T, et al.: Age and psychological influences on immune responses to trivalent inactivated influenza vaccine in the meditation or exercise for preventing acute respiratory infection (MEPARI) trial, *Hum Vaccin Immunother* 10(1), 2013.
- Obasi CN, Brown R, Ewers T, Barlow S, Gassman M, Zgierska A, et al.: Advantage of meditation over exercise in reducing cold and flu illness is related to improved function and quality of life, *Influenza Other Respi Viruses*, 2012.
- Rakel D, Mundt M, Ewers T, Fortney L, Zgierska A, Gassman M, et al.: Value associated with mindfulness meditation and moderate exercise intervention in acute respiratory infection: the MEPARI Study, *Fam Pract*, 2013.
- Zgierska A, Obasi CN, Brown R, Ewers T, Muller D, Gassman M, et al.: Randomized controlled trial of mindfulness meditation and exercise for the prevention of acute respiratory infection: possible mechanisms of action, *Evid Based Complement Alternat Med* 2013:952716, 2013.
- Barrett B, Locken K, Maberry R, Schwamman J, Bobula J, Brown R, et al.: The wisconsin upper respiratory symptom survey: development of an instrument to measure the common cold, *J Fam Pract* 51(3):265–273, 2002.
- Eccles R: Understanding the symptoms of the common cold and influenza, *Lancet Infect Dis* 5(11):718–725, 2005.
- Gwaltney JM: Clinical significance and pathogenesis of viral respiratory infections, *Am J Med* 112, 2002. Suppl-18S.
- Linder JA, Singer DE: Health-related quality of life of adults with upper respiratory tract infections, *J Gen Intern Med* 18(10):802–807, 2003.
- Barrett B, Brown RL, Mundt MP, Safdar N, Dye L, Maberry R, et al.: The wisconsin upper respiratory symptom survey is responsive, reliable, and valid, *J Clin Epidemiol* 58:609–617, 2005.
- Gwaltney JM: Rhinovirus infection of the normal human airway, *AM J Respir Crit Care Med* 152:536–539, 1995.
- Douglas RG, Alford RH, Cate TR, Couch RB: The leukocyte response during viral respiratory illness in man, *Ann Intern Med* 64(3):521–530, 1966.
- Garofalo R, Patel JA, Sim C, Schmalstieg FC, Goldman AS: Production of cytokines by virus-infected human respiratory epithelial cells, *J Allergy Clin Immunol* 91:177, 1993.
- Gern JE, Vrtis R, Kelly EAB, Dick EC, Busse WW: Rhinovirus produces nonspecific activation of lymphocytes through a monocyte-dependent mechanism, *J Immunol* 157:1605–1612, 1996.
- Baraniuk JN: Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa, *J Allergy Clin Immunol* 90(6):1045–1050, 1992.
- Gern JE, Busse WW: The role of viral infections in the natural history of asthma, *J Allergy Clin Immunol* 106:201–212, 2000.
- Gwaltney JM: Rhinoviruses. In Evans AS, Kaslow RA, editors: *Viral infections of humans: epidemiology and control*, ed 4, New York, 1997, Plenum Medical Book Company, pp 815–838.
- Arruda E, Pitkäranta A, Witek TJ, Doyle CA, Hayden FG: Frequency and history of rhinovirus infections in adults during autumn, *J Clin Microbiol* 35(11):2864–2868, 1997.

50. Pitkaranta A, Hayden FG: Rhinoviruses: important respiratory pathogens, *Ann Med* 30(6):529–537, 1998.
51. Heikkinen T, Jarvinen A: The common cold, *Lancet* 361(9351):51–59, 2003.
52. Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingssterhaus JM, Edwards KM, et al.: Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children, *NEJM* 350(5):443–450, 2004.
53. Sloots TP, Mackay IM, Bialasiewicz S, Jacob KC, McQueen E, Harnett GB, et al.: Human metapneumovirus, Australia, 2001–2004, *Emerg Infect Dis* 12(8):1263–1266, 2006.
54. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B: Cloning of a human parvovirus by molecular screening of respiratory tract samples, *Proc Natl Acad Sci U S A* 102(36):12891–12896, 2005.
55. Ma X, Endo R, Ishiguro N, Ebihara T, Ishiko H, Ariga T, et al.: Detection of human bocavirus in Japanese children with lower respiratory tract infections, *J Clin Microbiol* 44(3):1132–1134, 2006.
56. Sloots TP, McErlean P, Speicher DJ, Arden KE, Nissen MD, Mackay IM: Evidence of human coronavirus HKU1 and human bocavirus in Australian children, *J Clin Virol* 35(1):99–102, 2006.
57. Bradley-Stewart A, Jolly L, Adamson W, Gunson R, Frew-Gillespie C, Templeton K, et al.: Cytokine responses in patients with mild or severe influenza A(H1N1)pdm09, *J Clin Virol* 58(1):100–107, 2013.
58. Carrat F, Vergu E, Ferguson NM, Lemaître M, Cauchemez S, Leach S, et al.: Time lines of infection and disease in human influenza: a review of volunteer challenge studies, *Am J Epidemiol* 167(7):775–785, 2008.
59. Doyle WJ, Skoner DP, White M, Hayden F, Kaplan AP, Kaliner MA, et al.: Pattern of nasal secretions during experimental influenza virus infection, *Rhinology* 34(1):2–8, 1996.
60. Ebell MH, Alfonso A: A systematic review of clinical prediction rules for the diagnosis of influenza, *Ann Fam Med* 9(1):61–77, 2011.
61. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J: Clinical signs and symptoms predicting influenza infection, *Arch Intern Med* 160(21):3243–3247, 2000.
62. Smolderen KG, Vingerhoets AJ, Croon MA, Denollet J: Personality, psychological stress, and self-reported influenza symptomatology, *BMC Public Health* 7:339, 2007.
63. Advisory Committee on Immunization Practices CfDcAP: Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Morb Mortal Wkly Rep* 55:1–41, 2006.
64. Ball TM, Holberg CJ, Aldous MB, Martinez FD, Wright AL: Influence of attendance at day care on the common cold from birth through 13 years of age, *Arch Pediatr Adolesc Med* 156(2):121–126, 2002.
65. Hurwitz EL, Gunn WJ, Pinsky PF, Schonberger LB: Risk of respiratory illness associated with day-care attendance: a nationwide study, *Pediatrics* 87(1):62–69, 1991.
66. Lee HK, Hwang IH, Kim SY, Pyo SY: The effect of exercise on prevention of the common cold: a meta-analysis of randomized controlled trial studies, *Korean J Fam Med* 35(3):119–126, 2014.
67. Nieman DC: Moderate exercise improves immunity and decreases illness rates, *Am J Lifestyle Mod*, 2012. In press.
68. Martin SA, Pence BD, Woods JA: Exercise and respiratory tract viral infections, *Exerc Sport Sci Rev* 37(4):157–164, 2009.
69. Adam Y, Meinschmidt G, Lieb R: Associations between mental disorders and the common cold in adults: a population-based cross-sectional study, *J Psychosom Res* 74(1):69–73, 2013.
70. Maxwell L, Barrett B, Chase JC, Brown RL, Ewers T: Self-reported mental health predicts acute respiratory infection, *WJM* 16–20, 2015 June.
71. Cobb JM, Steptoe A: Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample, *Psychosomatic Medicine* 58(5):404–412, 1996.
72. Fondell E, Lagerros YT, Sundberg CJ, Lekander M, Balter O, Rothman KJ, et al.: Physical activity, stress, and self-reported upper respiratory tract infection, *Med Sci Sports Exerc* 43(2):272–279, 2011.
73. Graham NM, Douglas RM, Ryan P: Stress and acute respiratory infection, *Am J Epidemiol* 124(3):389–401, 1986.
74. Cohen S, Tyrell DAJ, Smith AP: Psychological stress and susceptibility to the common cold, *NEJM* 325:606–612, 1991.
75. Cohen S, Tyrell DAJ, Smith AP: Negative life events, perceived stress, negative affect, and susceptibility to the common cold, *J Pers Soc Psychol* 64(1):131–140, 1993.
76. Cohen S, Frank E, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM: Types of stressors that increase susceptibility to the common cold in healthy adults, *Health Psychology* 17(3):214–223, 1998.
77. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP: Childhood socioeconomic status and host resistance to infectious illness in adulthood, *Psychosomatic Medicine* 66(4):553–558, 2004.
78. Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM: Social ties and susceptibility to the common cold, *JAMA* 277(24):1940–1944, 1997.
79. Cohen S, Doyle WJ, Turner RB, Alper CM, Skoner DP: Emotional style and susceptibility to the common cold, *Psychosomatic Medicine* 65(4):652–657, 2003.
80. Cohen S, Doyle WJ, Skoner DP, Fireman P, Gwaltney JM, Newsom JT: State and trait negative affect as predictors of objective and subjective symptoms of respiratory viral infections, *J Pers Soc Psychol* 68(1):159–169, 1995.
81. Doyle WJ, Gentile DA, Cohen S: Emotional style, nasal cytokines, and illness expression after experimental rhinovirus exposure, *Brain Behav Immun* 20(2):175–181, 2006.
82. Mohren DCL, Swaen GMH, Borm PJA, Bast A, Galama JMD: Psychological job demands as a risk factor for common cold in a Dutch working population, *J Psychosom Res* 50(2001):21–27, 2001.
83. Stone AA, Bovbjerg DH, Neale JM, Napoli A, Valdimarsdottir H, Cox D, et al.: Development of common cold symptoms following experimental rhinovirus infection is related to prior stressful life events, *Behavioral Medicine* 18:115–120, 1992.
84. Takkouche B, Regueira C, Gestal-Otero JJ: A cohort study of stress and the common cold, *Epidemiology* 12(3):345–349, 2001.
85. Rakei D, Barrett B, Zhang Z, Hoefl T, Cheung B, Marchand L, et al.: Perception of empathy in the therapeutic encounter: effects on the common cold, *Patient Educ Couns* 85(3):390–397, 2011.
86. Nahas R, Balla A: Complementary and alternative medicine for prevention and treatment of the common cold, *Can Fam Physician* 57(1):31–36, 2011.
87. Moerman DE: The medicinal flora of native North America: an analysis, *J Ethnopharmacol* 31:1–42, 1991.
88. Schultes RE, von Reis S: *Ethnobotany: evolution of a discipline*, Portland, Oregon, 1995, Dioscorides Press, p 414.
89. Farnsworth NR: The role of ethnopharmacology in drug development. In Chadwick D, Marsh J, editors: *Bioactive compounds from plants (Ciba Symposium 154)*, New York & Chichester, England, 1990, Wiley.
90. Barrett B, Kiefer D: Medicinal plants, science, and health care, *J Herbs Spices Med Plants* 8(2):1–36, 2001.
91. Singha PK, Roy S, Dey S: Antimicrobial activity of *Andrographis paniculata*, *Fitoterapia* 74(7-8):692–694, 2003.
92. Hsu JH, Liou SS, Yu BC, Cheng JT, Wu YC: Activation of alpha1A-adrenoceptor by andrographolide to increase glucose uptake in cultured myoblast C2C12 cells, *Planta Medica* 70(12):1230–1233, 2004.
93. Yu BC, Hung CR, Chen WC, Cheng JT: Antihyperglycemic effect of andrographolide in streptozotocin-induced diabetic rats, *Planta Medica* 69(12):1075–1079, 2003.
94. Xia YF, Ye BQ, Li YD, Wang JG, He XJ, Lin X, et al.: Andrographolide attenuates inflammation by inhibition of NF-kappa B activation through covalent modification of reduced cysteine 62 of p50, *J Immunol* 173(6):4207–4217, 2004.
95. Burgos RA, Seguel K, Perez M, Meneses A, Ortega M, Guarda MI, et al.: Andrographolide inhibits IFN-gamma and IL-2 cytokine production and protects against cell apoptosis, *Planta Medica* 71(5):429–434, 2005.
96. Iruretagoyena MI, Tobar JA, Gonzalez PA, Sepulveda SE, Figueroa CA, Burgos RA, et al.: Andrographolide interferes with T cell activation and reduces experimental autoimmune encephalomyelitis in the mouse, *J Pharmacol & Exp Ther* 312(1):366–372, 2005.
97. Mandal SC, Dhara AK, Maiti BC: Studies in psychopharmacological activity of *Andrographis paniculata* extract, *Phytother Res* 15:253–256, 2001.
98. Kishore PH, Reddy MV, Reddy MK, Gunasekar D, Caux C, Bodo B: Flavonoids from *Andrographis lineata*, *Phytochemistry* 63(4):457–461, 2003.

99. Caceres DD, Hancke JL, Burgos RA, Sandberg F, Wikman GK: Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized *Andrographis paniculata* extract SHA-10 in reducing the symptoms of common cold. A randomized double blind-placebo study, *Phytomedicine* 6(4):217–223, 1999.
100. Gabrielian ES, Shukarian AK, Goukasova GI, Chandanian GL, Panossian AG, Wikman G, et al.: A double blind, placebo-controlled study of *Andrographis paniculata* fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis, *Phytomedicine* 9(7):589–597, 2002.
101. Hancke JA: Double-blind study with a new monodrug Kan Jang: decrease of symptoms and improvement in the recovery from common colds, *Phytotherapy Research* 9(8):559–562, 1995.
102. Melchior J: Controlled clinical study of standardized *Andrographis paniculata* extract in common cold - a pilot trial, *Phytomedicine* 3(4):315–318, 1997.
103. Melchior J, Spasov AA, Ostrovskij OV, Bulanov AE, Wikman G: Double-blind, placebo-controlled pilot and Phase III study of activity of standardized *Andrographis paniculata* Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection, *Phytomedicine* 7(5):341–350, 2000.
104. Spasov AA, Ostrovskij OV, Chernikov MV, Wikman G: Comparative controlled study of *Andrographis paniculata* fixed combination, Kan Jang and an Echinacea preparation as adjuvant, in the treatment of uncomplicated respiratory disease in children, *Phytotherapy Research* 18(1):47–53, 2004.
105. Shakhova EG, Spasov AA, Ostrovskii OV, Konovalova IV, Chernikov MV, Mel'nikova GI: Effectiveness of using the drug Kan-Yang in children with acute respiratory viral infection (clinical-functional data), [Russian], *Vestnik otorinolaringologii* (3)48–50, 2003.
106. Thamlikitkul V: Efficacy of *Andrographis paniculata*, Nees for pharyngotonsillitis in adults, *J Med Assoc Thailand = Chotmaibet thangphaet* 74(10):437–442, 1991.
107. Coon JT, Ernst E: *Andrographis paniculata* in the treatment of upper respiratory tract infections: a systematic review of safety and efficacy, *Planta Medica* 70(4):293–298, 2004.
108. Poolsup N, Suthisisang C, Prathanturug S, Asawamekin A, Chanchareon U: *Andrographis paniculata* in the symptomatic treatment of uncomplicated upper respiratory tract infection: systematic review of randomized controlled trials, *J Clin Pharm Ther* 29(1):37–45, 2004.
109. Saxena RC, Singh R, Kumar P, Yadav SC, Negi MP, Saxena VS, et al.: A randomized double blind placebo controlled clinical evaluation of extract of *Andrographis paniculata* (KalmCold) in patients with uncomplicated upper respiratory tract infection, *Phytomedicine* 17(3-4):178–185, 2010.
110. Upton R: *Astragalus Root: analytical, quality control, and therapeutic monograph*, Santa Cruz, CA, 1999, American Herbal Pharmacopoeia, pp 1–25.
111. McKenna D, Hughes K, Jones K: *Astragalus*, *Altern Ther Health Med* 8(6):34–40, 2002.
112. Chu DT, Wong WL, Mavligit GM: Immunotherapy with Chinese medicinal herbs. I. Immune restoration of local xenogeneic graft-versus-host reaction in cancer patients by fractionated *Astragalus membranaceus* in vitro, *J Clin Lab Immunol* 25(3):119–123, 1988.
113. Chu DT, Wong WL, Mavligit GM: Immunotherapy with Chinese medicinal herbs. II. Reversal of cyclophosphamide-induced immune suppression by administration of fractionated *Astragalus membranaceus* in vivo, *J Clin Lab Immunol* 25(3):125–129, 1988.
114. Sun Y, Hersh EM, Talpaz M, Lee SL, Wong W, Loo TL, et al.: Immune restoration and/or augmentation of local graft versus host reaction by traditional Chinese medicinal herbs, *Cancer* 52(1):70–73, 1983.
115. Tan BK, Vanitha J: Immunomodulatory and antimicrobial effects of some traditional Chinese medicinal herbs: a review, *Curr Med Chem* 11(11):1423–1430, 2004.
116. Block KI, Mead MN: Immune system effects of echinacea, ginseng, and astragalus: a review, *Integr Cancer Ther* 2(3):247–267, 2003.
117. Koenighofer M, Lion T, Bodenteich A, Prieschl-Grassauer E, Grassauer A, Unger H, et al.: Carrageenan nasal spray in virus confirmed common cold: individual patient data analysis of two randomized controlled trials, *Multidiscip Respir Med* 9(1):57, 2014.
118. Eccles R, Meier C, Jawad M, Weinmullner R, Grassauer A, Prieschl-Grassauer E: Efficacy and safety of an antiviral Iota-Carrageenan nasal spray: a randomized, double-blind, placebo-controlled exploratory study in volunteers with early symptoms of the common cold, *Respir Res* 11:108, 2010.
119. Fazekas T, Eickhoff P, Pruckner N, Vollhofer G, Fischmeister G, Diakos C, et al.: Lessons learned from a double-blind randomised placebo-controlled study with a iota-carrageenan nasal spray as medical device in children with acute symptoms of common cold, *BMC Complement Altern Med* 12:147, 2012.
120. Basch EM, Ulbricht CE: *Natural standard herb and supplement handbook: the bottom line*, St.Louis, 2005, Mosby.
121. Saller R, Beschomer M, Hellenbrecht D, et al.: Dose dependency of symptomatic relief of complaints by chamomile steam inhalation in patients with common cold, *Eur J Pharmacol* 183:728–729, 1990.
122. Reider N, Sepp N, Fritsch P, Weinlich G, Jensen-Jarolim E: Anaphylaxis to chamomile: clinical features and allergen cross-reactivity, *Clin Exp Allergy* 30(10):1436–1443, 2000.
123. Flannery MA: From Rudbeckia to Echinacea: the emergence of the purple cone flower in modern therapeutics, *Pharmacy in History* 41(2):52–59, 1999.
124. Brevoort P: The booming U.S. botanical market: a new overview, *HerbalGram* 44:33–46, 1998.
125. Karsch-Volk M, Barrett B, Kiefer D, Bauer R, Ardjomand-Woelkart K, Linde K: Echinacea for preventing and treating the common cold, *Cochrane Database Syst Rev* 2:CD000530, 2014.
126. Barrett B: Medicinal properties of *Echinacea*: a critical review, *Phytomedicine* 10(1):66–86, 2003.
127. American Herbal Pharmacopoeia: *Echinacea purpurea Root: standards of analysis, quality control, and therapeutics*, Santa Cruz, CA, 2004, American Herbal Pharmacopoeia.
128. American Herbal Pharmacopoeia: *Echinacea angustifolia Root: standards of analysis, quality control, and therapeutics*, Scotts Valley, CA, 2010, American Herbal Pharmacopoeia and Therapeutic Compendium.
129. Barnes J, Anderson LA, Gibbons S, Phillipson JD: Echinacea species (*Echinacea angustifolia* (DC.) Hell., *Echinacea pallida* (Nutt.) Nutt., *Echinacea purpurea* (L.) Moench): a review of their chemistry, pharmacology and clinical properties, *J Pharm Pharmacol* 57(8):929–954, 2005.
130. Bauer R: Chemistry, analysis and immunological investigations of Echinacea phytopharmaceuticals. In Wagner H, editor: *Immunomodulatory agents from plants*, Basel, Boston, Berlin, 1999, Birkhauser Verlag, pp 41–88.
131. Burger RA, Torres AR, Warren RP, Caldwell VD, Hughes BG: Echinacea-induced cytokine production by human macrophages, *Int J Immunopharmacol* 19(7):371–379, 1997.
132. Elsasser-Beile U, Willenbacher W, Bartsch HH, Gallati H, Schulte Monting J: Cytokine production in leukocyte cultures during therapy with Echinacea extract, *J Clin Lab Anal* 10:441–445, 1996.
133. Goel V, Chang C, Slama JV, Barton R, Bauer R, Gahler R, et al.: Alkylamides of Echinacea purpurea stimulate alveolar macrophage function in normal rats, *Int Immunopharmacol* 2(2-3):381–387, 2002.
134. Matthias A, Banbury L, Stevenson LM, Bone KM, Leach DN, Lehmann RP: Alkylamides from echinacea modulate induced immune responses in macrophages, *Immunol Invest* 36(2):117–130, 2007.
135. Melchart D, Linde K, Worku F, Sarkady L, Holzmann M, Jurcic K, et al.: Results of five randomized studies on the immunomodulatory activity of preparations of Echinacea, *J Altern Complement Med* 1(2):145–160, 1995.
136. Mishima S, Saito K, Maruyama H, Inoue M, Yamashita T, Ishida T, et al.: Antioxidant and immuno-enhancing effects of Echinacea purpurea, *Biological & Pharmaceutical Bulletin* 27(7):1004–1009, 2004.
137. Rehman J, Dillow JM, Carter SM, Chou J, Le B, Maisel AS: Increased production of antigen-specific immunoglobulins G and M following in vivo treatment with the medicinal plants *Echinacea angustifolia* and *Hydrastis canadensis*, *Immunology Letters* 68:391–395, 1999.
138. Dietz B, Heilmann J, Bauer R: Absorption of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides after oral application of Echinacea purpurea tincture, *Planta Medica* 67(9):863–864, 2001.

139. Matthias A, Addison RS, Penman KG, Dickinson RG, Bone KM, Lehmann RP: Echinacea alkamide disposition and pharmacokinetics in humans after tablet ingestion, *Life Sciences* 77(16):2018–2029, 2005.
140. Huntley AL, Thompson CJ, Ernst E: The safety of herbal medicinal products derived from echinacea species: a systematic review, *Drug Safety* 28(5):387–400, 2005.
141. Bräunig B, Dorn M, Limburg E, Knick E: Bausendorf. *Echinacea purpureae* radix: zur stärkung der körpereigenen abwehr bei grippalen infekten [Strengthening of the endogenous resistance to influenzal infections. Translation by Ralph McElroy Co., Austin TX], *Zeitschrift für Phytotherapie* 13:7–13, 1992.
142. Bräunig B, Knick E: Therapeutische Erfahrungen mit *Echinacea pallida* bei grippalen Infekten, *Naturheilpraxis* 1:72–75, 1993.
143. Brinkeborn RM, Shah DV, Degenring FH: Echinaforce® and other *Echinacea* fresh plant preparations in the treatment of the common cold, *Phytomedicine* 6(1):1–6, 1999.
144. Dorn M: Milderung grippaler Effekte durch ein pflanzliches Immunstimulans, *Natur- und Ganzheitsmedizin* 2:314–319, 1989.
145. Henneicke-von Zepelin HH, Hentschel C, Schnitker J, Kohlen R, Köhler G, Wüstenberg P: Efficacy and safety of a fixed combination phytomedicine in the treatment of the common cold (Acute viral respiratory tract infection): results of a randomized, double blind, placebo controlled, multicentre study, *Curr Med Res Opin* 15(3):214–227, 1999.
146. Hoheisel O, Sandberg M, Bertram S, Bulitta M, Schäfer M: Echinagard treatment shortens the course of the common cold: a double-blind, placebo-controlled clinical trial, *Eur J Clin Research* 9:261–268, 1997.
147. Scaglione F, Lund B: Efficacy in the treatment of the common cold of a preparation containing an Echinacea extract, *Int J Immunotherapy* 11(4):163–166, 1995.
148. Schulten B, Bulitta M, Ballering-Brühl B, Köster U, Schäfer M: Efficacy of *Echinacea purpurea* in patients with a common cold: a placebo-controlled, randomized, double-blind clinical trial, *Arzneim - Forsch/Drug Res* 51(11):563–568, 2001.
149. Cohen HA, Varsano I, Kahan E, Sarrell EM, Uziel Y: Effectiveness of an herbal preparation containing Echinacea, Propolis, and Vitamin C in preventing respiratory tract infections in children: a randomized, double-blind, placebo-controlled, multicenter study, *Arch Pediatr Adolesc Med* 158(3):217–221, 2004.
150. Goel V, Lovlin R, Barton R, Lyon MR, Bauer R, Lee TD, et al.: Efficacy of a standardized echinacea preparation (Echinilin) for the treatment of the common cold: a randomized, double-blind, placebo-controlled trial, *J Clin Pharm Ther* 29(1):75–83, 2004.
151. O'Neil J, Hughes S, Lourie A, Zweifler J: Effects of echinacea on the frequency of upper respiratory tract symptoms: a randomized, double-blind, placebo-controlled trial, *Ann Allergy Asthma Immunol* 100(4):384–388, 2008.
152. Taylor JA, Weber W, Standish L, Quinn H, Goesling J, McGann M, et al.: Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial, *JAMA* 290(21):2824–2830, 2003.
153. Yale SH, Liu K: Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial, *Arch Int Med* 164(11):1237–1241, 2004.
154. Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D: Treatment of the common cold with unrefined echinacea: a randomized, double-blind, placebo-controlled trial, *Ann Intern Med* 137(12):939–946, 2002.
155. Barrett B, Brown R, Rakel D, Mundt M, Bone K, Barlow S, et al.: Echinacea for treating the common cold: a randomized controlled trial, *Ann Intern Med*, 2010. In press.
156. Karsch-Volk M, Barrett B, Linde K: Echinacea for preventing and treating the common cold, *JAMA* 313(6):618–619, 2015.
157. Barrett B: Medicinal properties of echinacea: a critical review, *Phytomedicine* 10(1):66–86, 2003.
158. Barrett B: Echinacea: a safety review, *HerbalGram* 57:36–39, 2003.
159. Linde K, Barrett B, Wolkart K, Bauer R, Melchart D: Echinacea for preventing and treating the common cold, *Cochrane Database Syst Rev* (1):CD000530, 2006.
160. Giles JT, Palat CT, Chien SH, Chang ZG, Kennedy DT: Evaluation of Echinacea for treatment of the common cold, *Pharmacotherapy* 20(6):690–697, 2000.
161. Islam J, Carter R: Use of Echinacea in upper respiratory tract infection, *South Med J* 98(3):311–318, 2005.
162. Melchart D, Linde K, Fischer P, Kaesmayr J: Echinacea for preventing and treating the common cold, *Cochrane Database Syst Rev* (1), 2003.
163. Shah SA, Sander S, White CM, Rinaldi M, Coleman CI: Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis, *Lancet Infect Dis* 7(7):473–480, 2007.
164. Raus K, Pleschka S, Schop P, Fisher P: Echinaforce Hotdrink versus Oseltamivir in Influenza: a randomized, double-blind, double dummy, multicenter, non-inferiority clinical trial, *Current Therapeutic Research*, 2015. <http://dx.doi.org/10.1016/j.curtheres.2015.04.001>.
165. Caruso TJ, Gwaltney Jr JM: Treatment of the common cold with echinacea: a structured review, *Clin Infect Dis* 40(6):807–810, 2005.
166. Barrett B, Brown R, Rakel D, Rabago D, Marchand L, Scheder J, et al.: Placebo effects and the common cold: a randomized controlled trial, *Ann Fam Med* 9(4):312–322, 2011.
167. Agnew LL, Guffogg SP, Matthias A, Lehmann RP, Bone KM, Watson K: Echinacea intake induces an immune response through altered expression of leucocyte hsp70, increased white cell counts and improved erythrocyte antioxidant defences, *J Clin Pharm Ther* 30(4):363–369, 2005.
168. Woelkart K, Xu W, Pei Y, Makriyannis A, Picone RP, Bauer R: The endocannabinoid system as a target for alkamides from echinacea angustifolia roots, *Planta Medica* 71(8):701–705, 2005.
169. Taylor D: Kinship and Social Structure of the Island Carib, *Southwest J Anthrop* 2:180–212, 1946.
170. Gallo M, Sarkar M, Au W, Pietrzak K, Comas B, Smith M, et al.: Pregnancy outcome following gestational exposure to Echinacea, *Arch Intern Med* 160:3141–3143, 2000.
171. Harokopakis E, Albzreh MH, Haase EM, Scannapieco FA, Hajishengallis G: Inhibition of proinflammatory activities of major periodontal pathogens by aqueous extracts from elder flower (*Sambucus nigra*), *J Periodontol* 77(2):271–279, 2006.
172. Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, et al.: Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama, *J Altern Complement Med* 1(4):361–369, 1995.
173. Krawitz C, Mraheil MA, Stein M, Imirzalioglu C, Domann E, Pleschka S, et al.: Inhibitory activity of a standardized elderberry liquid extract against clinically-relevant human respiratory bacterial pathogens and influenza A and B viruses, *BMC Complement Altern Med* 11:16, 2011.
174. Zakay-Rones Z, Thom E, Wollan T, Wadstein J: Randomized study of the efficacy and safety of oral elderberry extract in the treatment of influenza A and B virus infections, *J Int Med Res* 32(2):132–140, 2004.
175. Centre for Reviews and Dissemination: Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials (Structured abstract), *Database of Abstracts of Reviews of Effectiveness* 3(3), 2005.
176. Cicero AF, Ferroni A, Ertek S: Tolerability and safety of commonly used dietary supplements and nutraceuticals with lipid-lowering effects, *Expert Opin Drug Saf* 11(5):753–766, 2012.
177. Mulrow C, Lawrence V, Ackermann R, et al.: *Garlic: effects on cardiovascular risks and disease, protective effects against cancer, and clinical adverse effects: summary*, Publication No. 01–E022. Rockville MD, 2000, Agency for Healthcare Research and Quality. Evidence Report / Technology Assessment.
178. Stevinson C, Pittler MH, Ernst E: Garlic for treating hypercholesterolemia: a meta-analysis of randomized clinical trials, *Ann Intern Med* 133:420–429, 2000.
179. Lissiman E, Bhasale AL, Cohen M: Garlic for the common cold, *Cochrane Database Syst Rev* 11:CD006206, 2014.
180. Josling P: Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey, *Advances in Therapy* 18(4):189–193, 2001.
181. Center for Reviews and Dissemination Reviewers: Efficacy of ginger for nausea and vomiting: a systematic review of randomized clinical trials, *Database of Abstracts of Reviews of Effectiveness December* (4), 2002.
182. Matthews A, Haas DM, O'Mathuna DP, Dowswell T, Doyle M: Interventions for nausea and vomiting in early pregnancy, *Cochrane Database Syst Rev* 3:CD007575, 2014.

183. Borrelli F, Capasso R, Aviello G, Pittler MH, Izzo AA: Effectiveness and safety of ginger in the treatment of pregnancy-induced nausea and vomiting, *Obstet Gynecol* 105(4):849–856, 2005.
184. Grontved A, Hentzer E: Vertigo-reducing effect of ginger root. A controlled clinical study, *Orl; Journal of Oto-Rhino-Laryngology & its Related Specialties* 48(5):282–286, 1986.
185. Jenabi E: The effect of ginger for relieving of primary dysmenorrhoea, *J Pak Med Assoc* 63(1):8–10, 2013.
186. Kashefi F, Khajehei M, Alavinia M, Golmakani E, Asili J: Effect of ginger (*Zingiber officinale*) on heavy menstrual bleeding: a placebo-controlled, randomized clinical trial, *Phytother Res* 29(1):114–119, 2015.
187. Ozgoli G, Goli M, Moattar F: Comparison of effects of ginger, mefenamic acid, and ibuprofen on pain in women with primary dysmenorrhea, *J Altern Complement Med* 15(2):129–132, 2009.
188. Altman RD, Marcussen KC: Effects of a ginger extract on knee pain in patients with osteoarthritis, *Arthritis & Rheumatism* 44(11):2531–2538, 2001.
189. Guay J, Champagne P, Guibord P, Gruenwald J: The efficacy and safety of a patent pending combination of ginger and goldenrod extracts on the management of cold symptoms: a randomized, double-blind controlled trial, *Food and Nutrition Sciences* 3:1651–1657, 2012.
190. Kaptchuk TJ: *The Web That Has No Weaver: understanding Chinese Medicine*, ed 2, New York & London, 2000, Contemporary Books, McGraw Hill.
191. Kiefer D, Pantuso T: Panax ginseng, *Am Fam Physician* 68(8):1539–1542, 2003.
192. Panossian A, Wikman G, Wagner H: Plant adaptogens III. Earlier and more recent aspects and concepts on their mode of action, *Phytotherapy* 6(4):287–300, 1999.
193. Wagner H: Immunostimulants and adaptogens from plants. In Arnason JT, Mata R, Romeo JT, editors: *Phytochemistry of medical plants*, New York, 1995, Plenum Press, pp 1–18.
194. Scaglione F, Cattaneo G, Alessandria M, Cogo R: Efficacy and safety of the standardized ginseng extract G 115 for potentiating vaccination against common cold and/or influenza syndrome, *Drugs Exptl Clin Res* 22(2):65–72, 1996.
195. Lee CS, Lee JH, Oh M, Choi KM, Jeong MR, Park JD, et al.: Preventive effect of Korean red ginseng for acute respiratory illness: a randomized and double-blind clinical trial, *J Korean Med Sci* 27(12):1472–1478, 2012.
196. McElhanev JE, Goel V, Toane B, Hooten J, Shan JJ: Efficacy of COLD-FX in the prevention of respiratory symptoms in community-dwelling adults: a randomized, double-blinded, placebo controlled trial, *J Altern Complement Med* 12(2):153–157, 2006.
197. Immune modulating effects of daily supplementation of COLD-FX (a proprietary extract of North American ginseng) in healthy adults, 2006.
198. Wang M, Guilbert LJ, Li J, Wu Y, Pang P, Basu TK, et al.: A proprietary extract from North American ginseng (*Panax quinquefolium*) enhances IL-2 and IFN-gamma productions in murine spleen cells induced by Con-A, *Int Immunopharmacol* 4(2):311–315, 2004.
199. McElhanev JE, Gravenstein S, Cole SK, Davidson E, O'Neill D, Petitjean S, et al.: A placebo-controlled trial of a proprietary extract of North American ginseng (CVT-E002) to prevent acute respiratory illness in institutionalized older adults, *J Am Geriatr Soc* 52(1):13–19, 2004.
200. Predy GN, Goel V, Lovlin R, Donner A, Stitt L, Basu TK: Efficacy of an extract of North American ginseng containing poly-furanosyl-pyranosyl-saccharides for preventing upper respiratory tract infections: a randomized controlled trial, *CMAJ* 173(9):1043–1048, 2005.
201. Seida JK, Durec T, Kuhle S: North American (*Panax quinquefolius*) and Asian Ginseng (*Panax ginseng*) preparations for prevention of the common cold in healthy adults: a systematic review, *Evid Based Complement Alternat Med* 2011:282151, 2011.
202. Jellin JM, Gregory PJ, Batz F, Hitchens K, et al.: *Pharmacist's Letter / Prescriber's Letter Natural Medicines Comprehensive Database*, ed 4, Stockton, CA, 2003, Therapeutic Research Faculty.
203. Blumenthal M, Hall T, Goldberg A, Kunz T, Dinda K, Brinckmann J, et al.: *The ABC Clinical Guide to Herbs*, Austin, TX, 2003, American Botanical Council.
204. Bladt S, Wagner H: From the Zulu medicine to the European phytomedicine Umckaloabo, *Phytotherapy* 14 (Suppl 6):2–4, 2007.
205. Brendler T, van Wyk BE: A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae), *J Ethnopharmacol* 119(3):420–433, 2008.
206. Kolodziej H: Aqueous ethanolic extract of the roots of *Pelargonium sidoides*—new scientific evidence for an old anti-infective phytopharmaceutical, *Planta Med* 74(6):661–666, 2008.
207. Moyo M, Van SJ: Medicinal properties and conservation of *Pelargonium sidoides* DC., *J Ethnopharmacol* 152(2):243–255, 2014.
208. Michaelis M, Doerr HW, Cinatl Jr J: Investigation of the influence of EPs(R) 7630, a herbal drug preparation from *Pelargonium sidoides*, on replication of a broad panel of respiratory viruses, *Phytotherapy* 18(5):384–386, 2011.
209. Theisen LL, Muller CP: EPs(R) 7630 (Umckaloabo(R)), an extract from *Pelargonium sidoides* roots, exerts anti-influenza virus activity in vitro and in vivo, *Antiviral Res* 94(2):147–156, 2012.
210. Lizogub VG, Riley DS, Heger M: Efficacy of a *Pelargonium sidoides* preparation in patients with the common cold: a randomized, double blind, placebo-controlled clinical trial, *Explore (NY)* 3(6):573–584, 2007.
211. Matthys H, Heger M: EPs 7630-solution—an effective therapeutic option in acute and exacerbating bronchitis, *Phytotherapy* 14 (Suppl 6):65–68, 2007.
212. Timmer A, Gunther J, Rucker G, Motschall E, Antes G, Kern WV: *Pelargonium sidoides* extract for acute respiratory tract infections, *Cochrane Database Syst Rev* (3):CD006323, 2008.
213. Timmer A, Gunther J, Motschall E, Rucker G, Antes G, Kern WV: *Pelargonium sidoides* extract for treating acute respiratory tract infections, *Cochrane Database Syst Rev* 10:CD006323, 2013.
214. Teschke R, Frenzel C, Wolff A, Herzog J, Glass X, Schulze J, et al.: Initially purported hepatotoxicity by *Pelargonium sidoides*: the dilemma of pharmacovigilance and proposals for improvement, *Ann Hepatol* 11(4):500–512, 2012.
215. de Boer HJ, Hagemann U, Bate J, Meyboom RH: Allergic reactions to medicines derived from *Pelargonium* species, *Drug Saf* 30(8):677–680, 2007.
216. Rennard BO, Ertl RF, Gossman GL, Robbins RA, Rennard SI: Chicken soup inhibits neutrophil chemotaxis in vitro, *Chest* 118:1150–1157, 2000.
217. Saketkhoo K, Januszkiewicz A, Sackner MA: Effects of drinking hot water, cold water, and chicken soup on nasal mucus velocity and nasal airflow resistance, *Chest* 74(4):408–410, 1978.
218. Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE: Honey for acute cough in children, *Cochrane Database Syst Rev* 3:CD007094, 2012.
219. Cohen HA, Rozen J, Kristal H, Laks Y, Berkovitch M, Uziel Y, et al.: Effect of honey on nocturnal cough and sleep quality: a double-blind, randomized, placebo-controlled study, *Pediatrics* 130(3):465–471, 2012.
220. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR: A comparison of the effect of honey, dextromethorphan, and diphenhydramine on nightly cough and sleep quality in children and their parents, *J Altern Complement Med* 16(7):787–793, 2010.
221. Ernst E, Pecho E, Wirz P, Saradeth T: Regular sauna bathing and the incidence of common colds, *Ann Med* 22(4):225–227, 1990.
222. Pach D, Knochel B, Ludtke R, Wruck K, Willich SN, Witt CM: Visiting a sauna: does inhaling hot dry air reduce common cold symptoms? A randomised controlled trial, *Med J Aust* 193(11–12):730–734, 2010.
223. Singh M, Singh M: Heated, humidified air for the common cold, *Cochrane Database Syst Rev* 6:CD001728, 2013.
224. Takkouche B, Regueira-Mendez C, Garcia-Closas R, Figueiras A, Gestal-Otero JJ, Hernan MA: Intake of wine, beer, and spirits and the risk of clinical common cold, *Am J Epidemiol* 155(9):853–858, 2002.
225. Rabago D, Zgierska A, Mundt M, Barrett B, Bobula J, Maberry R: Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial, *J Fam Pract* 51(12):1049–1055, 2002.
226. King D, Mitchell B, Williams CP, Spurling GK: Saline nasal irrigation for acute upper respiratory tract infections, *Cochrane Database Syst Rev* 4:CD006821, 2015.
227. Adam P, Stiffman M, Blake RL: A clinical trial of hypertonic saline nasal spray in subjects with the common cold or rhinosinusitis, *Arch Fam Med* 7:39–43, 1998.

228. Diamond L, Dockhorn RJ, Grossman J, Kisicki JC, Posner M, Zinny MA, et al.: A dose-response study of the efficacy and safety of ipratropium bromide nasal spray in the treatment of the common cold, *J Allergy Clin Immunol* 95:1139–1146, 1995.
229. Szajewska H, Ruszczynski M, Radzikowski A: Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials, *J Pediatr* 149(3):367–372, 2006.
230. Camilleri M: Probiotics and irritable bowel syndrome: rationale, mechanisms, and efficacy, *J Clin Gastroenterol* 42 (Suppl 3 Pt 1) S123–S125, 2008.
231. Ford AC, Talley NJ, Quigley EM, Moayyedi P: Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials, *Dis Colon Rectum* 52(10):1805, 2009.
232. Moayyedi P, Ford AC, Talley NJ, Cremonini F, Foxx-Orenstein AE, Brandt LJ, et al.: The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review, *Gut* 59(3):325–332, 2010.
233. Nikfar S, Rahimi R, Rahimi F, Derakhshani S, Abdollahi M: Efficacy of probiotics in irritable bowel syndrome: a meta-analysis of randomized, controlled trials, *Dis Colon Rectum* 51(12):1775–1780, 2008.
234. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE: Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials, *Lancet Infect Dis* 6(6):374–382, 2006.
235. Berggren A, Lazou AI, Larsson N, Onning G: Randomised, double-blind and placebo-controlled study using new probiotic lactobacilli for strengthening the body immune defence against viral infections, *Eur J Nutr*, 2010.
236. West NP, Pyne DB, Cripps AW, Hopkins WG, Eskesen DC, Jairath A, et al.: Lactobacillus fermentum (PCC(R)) supplementation and gastrointestinal and respiratory-tract illness symptoms: a randomised control trial in athletes, *Nutr J* 10:30, 2011.
237. Langkamp-Henken B, Rowe CC, Ford AL, Christman MC, Nieves Jr C, Khouri L, et al.: Bifidobacterium bifidum R0071 results in a greater proportion of healthy days and a lower percentage of academically stressed students reporting a day of cold/flu: a randomised, double-blind, placebo-controlled study, *Br J Nutr* 113(3):426–434, 2015.
238. de Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al.: Probiotic bacteria reduced duration and severity but not the incidence of common cold episodes in a double blind, randomized, controlled trial, *Vaccine* 24(44-46):6670–6674, 2006.
239. Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC: Probiotic effects on cold and influenza-like symptom incidence and duration in children, *Pediatrics* 124(2):e172–e179, 2009.
240. Makino S, Ikegami S, Kume A, Horiuchi H, Sasaki H, Orii N: Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1, *Br J Nutr* 104(7):998–1006, 2010.
241. Merenstein D, Whittaker C, Chadwell T, Wegner B, D'Amico F: Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial, *J Fam Pract* 54(2):144–151, 2005.
242. Merenstein DJ, Foster J, D'Amico F: A randomized clinical trial measuring the influence of kefir on antibiotic-associated diarrhea: the measuring the influence of Kefir (MILK) Study, *Arch Pediatr Adolesc Med* 163(8):750–754, 2009.
243. Smith T: *Probiotics and respiratory tract infections: an annotated bibliography*, [dissertation]. Newark, NJ, 2010, University of Medicine and Dentistry of New Jersey.
244. King S, Glanville J, Sanders ME, Fitzgerald A, Varley D: Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis, *Br J Nutr* 112(1):41–54, 2014.
245. Kang EJ, Kim SY, Hwang IH, Ji YJ: The effect of probiotics on prevention of common cold: a meta-analysis of randomized controlled trial studies, *Korean J Fam Med* 34(1):2–10, 2013.
246. Pauling L: The significance of the evidence about ascorbic acid and the common cold, *PNAS* 68(11):2678–2681, 1971.
247. Anderson TW, Reid DBW, Beaton GH: Vitamin C and the common Cold: a double-blind Trial, *CMAJ* 107:503–508, 1972.
248. Anderson TW, Suranyi G, Beaton GH: The effect on winter illness of large doses of vitamin C, *CMAJ* 111:31–36, 1974.
249. Anderson TW, Beaton GH, Corey PN, Spero L: Winter illness and Vitamin C: the effect of relatively low doses, *CMAJ* 112:823–826, 1975.
250. Hemila H, Chalker E: Vitamin C for preventing and treating the common cold, *Cochrane Database Syst Rev* 1:CD000980, 2013.
251. Douglas RM, Hemila H, Chalker E, D'Souza RRD, Treacy B: Vitamin C for preventing and treating the common cold, *Cochrane Database Syst Rev* (1), 2006.
252. Hemila H: Does Vitamin C alleviate the symptoms of the common cold? - A review of current evidence, *Scand J Infect Dis* 26:1–6, 1994.
253. Chalmers TC: Effects of ascorbic acid on the common cold, *Am J Med* 58:532–536, 1975.
254. Borella E, Neshet G, Israeli E, Shoenfeld Y: Vitamin D: a new anti-infective agent? *Ann NY Acad Sci* 1317:76–83, 2014.
255. Murdoch DR, Slow S, Chambers ST, Jennings LC, Stewart AW, Priest PC, et al.: Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial, *JAMA* 308(13):1333–1339, 2012.
256. Linder JA: Vitamin D and the cure for the common cold, *JAMA* 308(13):1375–1376, 2012.
257. Eby GA, Davis DR, Halcomb WW: Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study, *Antimicrob Agents Chemother* 25(1):20–24, 1984.
258. Godfrey JC, Godfrey NJ, Novick SG: Zinc for treating the common cold: review of all clinical trials since 1984, *Alternative Therapies* 2(6):63–72, 1996.
259. Singh M, Das RR: Zinc for the common cold, *Cochrane Database Syst Rev* (2):CD001364, 2011.
260. Hulisz D: Efficacy of zinc against common cold viruses: an overview, *JAPhA* 44(5):594–603, 2004.
261. Marshall I: Zinc for the common cold, *Cochrane Database Syst Rev* 3:CD001364, 2006.
262. Farr BM, Hayden FG, Gwaltney JM: Zinc gluconate lozenges for treating the common cold, *Ann Intern Med* 126(9):738–739, 2001.
263. Jackson JL, Peterson C, Lesho E: A meta-analysis of zinc salt lozenges and the common cold, *Ann Intern Med* 157(10):2373–2376, 1997.
264. Hemila H: Zinc lozenges may shorten the duration of colds: a systematic review, *Open Respir Med J* 5:51–58, 2011.
265. Hemila H, Chalker E: The effectiveness of high dose zinc acetate lozenges on various common cold symptoms: a meta-analysis, *BMC Fam Pract* 16:24, 2015.
266. Salgueiro MJ, Zubillaga MB, Lysionek AE, Caro RA, Weill R, Boccio JR: The role of zinc in the growth and development of children, *Nutrition* 18(6):510–519, 2002.
267. Walker CF, Black RE: Zinc and the risk for infectious disease, *Annual Review of Nutrition* 25:25–275, 2004.
268. Jafek BW, Linschoten MR, Murrow BW: Anosmia after intranasal zinc gluconate use, *Am J Rhinol* 18(3):137–141, 2004.
269. Moerman DE, Jonas WB: Deconstructing the placebo effect and finding the meaning response, *Ann Intern Med* 136:471–476, 2002.
270. Barrett B, Muller D, Raket D, Rabago D, Marchand L, Scheder J: Placebo, meaning and health: *Perspect Biol Med* 49(2):178–198, 2006.
271. Barrett B, Raket D, Chewning B, Marchand L, Rabago D, Brown R, et al.: Rationale and methods for a trial assessing placebo, echinacea, and doctor-patient interaction in the common cold, *Explore (NY)* 3(6):561–572, 2007.
272. Kaptchuk TJ: The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance? *Ann Intern Med* 136(11):817–825, 2002.
273. Raket DP, Hoefft TJ, Barrett BP, Chewning BA, Craig BM, Niu M: Practitioner empathy and the duration of the common cold, *Fam Med* 41(7):494–501, 2009.
274. Smith MBH, Feldman W: Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991, *JAMA* 269(17):2258–2263, 1993.
275. De Sutter AIM, Lemiengre M, Campbell H, Mackinnon HF: Antihistamines for the common cold, *Cochrane Database Syst Rev* (4), 2004.

276. Doyle WJ, McBride TP, Skoner DP, Maddern BR, Gwaltney JM, Uhrin M: A double-blind, placebo-controlled clinical trial of the effect of chlorpheniramine on the response of the nasal airway, middle ear and eustachian tube to provocative rhinovirus challenge, *Pediatr Infect Dis J* 7:215–242, 1988.
277. Gwaltney JM, Park J, Paul RA, Edelman DA, O'Connor RA, Turner RB: Randomized controlled trial of clemastine fumarate for treatment of experimental rhinovirus colds, *Clin Infect Dis* 22:656–662, 1996.
278. Muether PS, Gwaltney Jr JM: Variant effect of first- and second-generation antihistamines as clues to their mechanism of action on the sneeze reflex in the common cold, *Clin Infect Dis* 33(9):1483–1488, 2001.
279. Loose I, Winkel M: Clinical, double-blind, placebo-controlled study investigating the combination of acetylsalicylic acid and pseudoephedrine for the symptomatic treatment of nasal congestion associated with common cold, *Arzneimittel-Forschung* 54(9):513–521, 2004.
280. Jawad SS, Eccles R: Effect of pseudoephedrine on nasal airflow in patients with nasal congestion associated with common cold, *Rhinology* 36(2):73–76, 1998.
281. Sperber SJ, Sorrentino JV, Riker DK, Hayden FG: Evaluation of an alpha agonist alone and in combination with a nonsteroidal antiinflammatory agent in the treatment of experimental rhinovirus colds, *Bulletin of N Y Academic Med* 65(1):145–159, 2000.
282. Taverner D, Danz C, Economos D: The effects of oral pseudoephedrine on nasal patency in the common cold: a double-blind single-dose placebo-controlled trial, *Clin Otolaryngol* 24:47–51, 1999.
283. Kernan WN, Viscoli CM, Brass L, Broderick JP, Brott T, Feldmann E, et al.: Phenylpropranolamine and the risk of hemorrhagic stroke, *NEJM* 343(25):1826–1832, 2001.
284. Akerlund A, Klint T, Olen L, Rundcrantz H: Nasal decongestant effect of oxymetazoline in the common cold: an objective dose-response study in 106 patients, *J Laryngol Otol* 103:743–746, 1989.
285. Morris S, Eccles R, Martez SJ, Riker DK, Witek TJ: An evaluation of nasal response following different treatment regimes of oxymetazoline with reference to rebound congestion, *Am J Rhinol* 11(2):109–115, 1997.
286. Taverner D, Latte J, Draper M: Nasal decongestants for the common cold, *Cochrane Database Syst Rev* (4), 2004.
287. Witek Jr TJ, Canestrari DA, Hernandez JR, Miller RD, Yang JY, Riker DK: Superficial nasal mucosal blood flow and nasal patency following topical oxymetazoline hydrochloride, *Ann Allergy* 68(2):165–168, 1992.
288. Anonymous: Lack of evidence exists for effectiveness of over-the-counter cough preparations for children with URTI, *ACP Journal Club November/December* 137(3):106, 2002.
289. Eccles R, Morris S, Jawad M: Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection, *J Clin Pharm Ther* 17(3):175–180, 1992.
290. Freestone C, Eccles R: Assessment of the antitussive efficacy of codeine in cough associated with common cold, *J Pharm Pharmacol* 49(10):1045–1049, 1997.
291. Schroeder K, Fahey T: Over-the-counter medications for acute cough in children and adults in ambulatory settings, *Cochrane Database Syst Rev* 2, 2004.
292. Graham NMH, Burrell CJ, Douglas RM, DeBelle PDL: Adverse effects of aspirin, acetaminophen, and ibuprofen on immune function, viral shedding, and clinical status in rhinovirus-infected volunteers, *J Infect Dis* 162:1277–1282, 1990.
293. Stanley ED, Jackson GG, Panusarn C, Rubenis M, Dirda V: Increased virus shedding with aspirin treatment of rhinovirus infection, *JAMA* 231(12):1248–1251, 1975.
294. Fries JF: NSAID gastropathy: the second most deadly rheumatic disease? Epidemiology and risk appraisal, *J Rheumatol* 28:6–10, 1991.
295. Andrade SE, Martinez C, Walker AM: Comparative safety evaluation of non-narcotic analgesics, *J Clin Epidemiol* 51(12):1357–1365, 1998.
296. Page J, Henry D: Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem, *Arch Intern Med* 160(6):777–784, 2000.
297. Borum P, Olsen L, Winther B, Mygind N: Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold, *Am Rev Respir Dis* 123:418–420, 1981.
298. Hayden FG, Diamond L, Wood PB, Korts DC, Wecker MT: Effectiveness and safety of intranasal ipratropium bromide in common colds, *Ann Intern Med* 125:89–97, 1996.
299. De Sutter AI, van Driel ML, Kumar AA, Lesslar O, Skrt A: Oral antihistamine-decongestant-analgesic combinations for the common cold, *Cochrane Database Syst Rev* 2:CD004976, 2012.
300. Gwaltney JM: Combined antiviral and antimediator treatment of rhinovirus colds, *J Infect Dis* 166:776–782, 1992.
301. Hayden FG, Hipskind GJ, Woerner DH, Eisen GF, Janssens M, Janssen PAJ, et al.: Intranasal pirodavir (R77,975) treatment of rhinovirus colds, *Antimicrob Agents Chemother* 39(2):290–294, 2000.
302. Hayden FG, Herrington DT, Coats TL, Kim K, Cooper EC, Villano SA, et al.: Efficacy and safety of oral pleconaril for treatment of colds due to picornaviruses in adults: results of 2 double-blind, randomized, placebo-controlled trials, *Clin Infect Dis* 36(12):1523–1532, 2003.
303. Turner RB, Wecker MT, Pohl G, Witek TJ, McNally E, George RS, et al.: Efficacy of tremacamra, a soluble intercellular adhesion molecule 1, for experimental rhinovirus infection, *JAMA* 281(19):1797–1804, 1999.
304. Jefferson TO, Tyrrell D: Antivirals for the common cold [Systematic Review], *Cochrane Database Syst Rev* (3), 2005.