



# NATURAL MEDICINE JOURNAL **RESEARCH GUIDE**

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## Clearing Up the **COLD AND FLU** Controversy

An evaluation of the efficacy  
of single ingredient support

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## Cold and Flu: Overview

The common cold is a viral infection of the upper respiratory tract, presenting with some combination of nasal congestion, sneezing, cough, sore throat, mild headache, low-grade fever, and general malaise. Influenza (the flu) presents in a similar way but with more sudden onset, greater intensity, higher fever, and body aches. Nausea and vomiting occasionally accompany the flu, but stomach symptoms are more likely to be caused by viral or bacterial gastroenteritis rather than the influenza virus.

Cases of the common cold and flu peak during fall and winter, with children under the age of 6 at particular risk for both illnesses and adults over the age of 65 at a higher risk for the flu. These airborne infections spread readily through groups of people in confined places like schools, nursing homes, or airplanes.

The common cold and flu are self-limiting, but potential complications include bronchitis, pneumonia, and asthma exacerbation. Patients at greatest risk for complications include those who are under the age of 2, over the age of 65, pregnant, obese, or have weakened immunity.

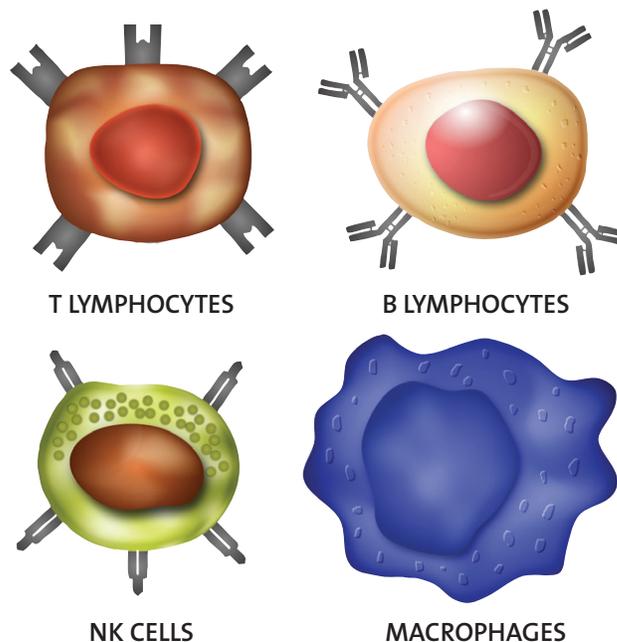
## The Immune Response

The rhinovirus is most often implicated in the common cold, and the influenza virus causes the flu. The skin and mucosal membranes create an initial barrier to infection, but if the virus successfully passes through these barriers, it will trigger a systemic immune response.

The immune response to a virus is classified into 2 parts: innate immunity and adaptive immunity. The innate immune response produces a rapid and non-specific response, mediated primarily by interferon, macrophages, natural killer (NK) cells, and the complement cascade. The adaptive immune response then mounts a more specific response. The most important aspects of the adaptive immune response to viruses are antibody production by B lymphocytes (the humoral response) and cytotoxic activity of T lymphocytes (the cell-mediated response).

The humoral immune response and the cell-mediated response both produce memory cells, establishing protection against subsequent infections. The reason that people get repeated colds and flus, however, is because of the many different types and strains of each virus. There are more than 100 different serotypes of the rhinovirus. There are 4 types of the influenza virus (A, B, C, and D), and influenza A is further categorized by 18

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different hemagglutinin subtypes (H1 through H18) and 11 different neuraminidase subtypes (N1 through N11).

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## Conventional Treatment and Prevention

Conventional treatment of the common cold and flu emphasizes rest, fluids, and over-the-counter medications to alleviate symptoms. Acetaminophen or ibuprofen suppress fever and relieve pain. Nasal decongestants and cough suppressants provide temporary symptomatic relief. None of these medications shorten the duration of illness.

Oseltamivir (Tamiflu) is a prescription antiviral that is FDA-approved to treat the flu. Tamiflu inhibits the neuraminidase enzyme, an enzyme that allows the release of viral particles from infected cells to spread through the respiratory tract. Neuraminidase inhibition traps virally infected cells in respiratory secretions and prevents their spread. A 2014 Cochrane review and

a 2015 meta-analysis published in the *Lancet* came to similar conclusions: Tamiflu reduces the duration of flu symptoms by ½ to 1 day. This benefit is achieved only if treatment begins within 48 hours of symptom onset, and treatment introduces the potential side effect of nausea and vomiting.

Given that conventional treatments do not strengthen innate or adaptive immune responses and have only limited efficacy, flu prevention is a public health priority. The Centers for Disease Control and Prevention (CDC) recommends that all people aged 6 months and older receive the seasonal flu vaccine every year. The efficacy of the flu vaccine varies from year to year, with the CDC reporting in February of 2017 that it is generally 50% to 60% effective at preventing the flu. Additional ways to prevent the common cold and flu include washing hands, keeping surrounding areas clean, avoiding others who are sick, and strengthening immunity with a healthy lifestyle.

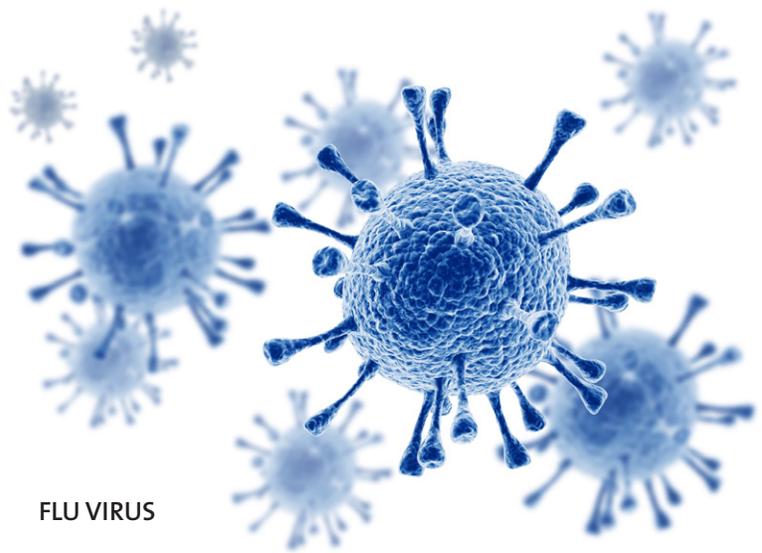
With a flu vaccine that is only 50% effective, antiviral medications that reduce duration of illness by 1 day at best, and over-the-counter medications that do no more than temporarily suppress symptoms, there is a clear need for more effective approaches to the common cold and flu. Many patients and clinicians are turning to natural therapies.

## The Controversy of Natural Therapies

The National Center for Complementary and Integrative Health, which is a division of the National Institutes of Health (NIH) hesitantly acknowledges that some dietary supplements have shown promise for treating the common cold, but they conclude that no evidence supports the use of any complementary health approach for the treatment or prevention of the flu.

Nevertheless, integrative clinicians recommend countless natural products to strengthen their patients' resilience through the cold and flu season. In addition, self-educated consumers flock to health food stores to purchase vitamin C, zinc, Echinacea, and elderberry to boost their immunity. Are patients and consumers wasting their money, or is there evidence to support the use of natural products for the cold and flu?

The following pages will evaluate the scientific basis for the use of natural products for the common cold and flu. We will address 3 clinical goals: proactive prevention, reduction of symptom severity, and reduction of symptom duration.



FLU VIRUS

## Antibiotic Resistance

The common cold and flu are viral infections. They are not caused by bacteria and cannot be treated with antibiotics. Although bacterial infections like pneumonia can complicate the flu, the routine administration of antibiotics to patients with the common cold or the flu is not recommended.

Since their discovery in the 1920s, antibiotics have saved countless lives. Unfortunately, the mere act of taking an antibiotic can create antibiotic-resistant bacteria in a person's digestive tract. Those resistant bacteria can then spread through hospitals or through the community.

According to data from 2010-2011 that was published in the *Journal of the American Medical Association (JAMA)*, more than 30% of antibiotic prescriptions given in the outpatient setting are unnecessary or inappropriate. Additional data published by the CDC suggest that this statistic may exceed 50%.

Overuse of antibiotics has created a worldwide problem of resistant infections that lead to severe illness, long hospitalizations, toxic medications, and even death. It is critical for practitioners to educate patients on the need to take antibiotics only when clinically necessary.

## Natural Therapies for Treatment and Prevention

There is no cure for the common cold or flu, but there are effective strategies for proactive prevention and for the reduction of symptom severity and duration. This section will review the scientific evidence for 7 herbal and nutritional supplements for the common cold and flu.

### Black Elderberry

Black elderberry (*Sambucus nigra*) has a long history of use for the common cold and flu. Extensive research confirms that it has antiviral activity against influenza A and B by reducing hemagglutination and inhibiting viral replication.

The ability of black elderberry to reduce the severity and duration of the flu has been demonstrated in 2 randomized, placebo-controlled trials. The first was conducted during an influenza outbreak in Panama in 1993. Complete resolution of symptoms was achieved within 2-3 days in 90% of the patients treated with black elderberry syrup, whereas those treated with placebo took 6 days to recover. The second study confirmed these findings in 2004, demonstrating that black elderberry decreased symptom duration by an average of 4 days in patients with influenza A or B.

Black elderberry may offer the additional benefit of reducing the risk of complications from upper respiratory viral infections. A 2011 study, published in *British Medical Journal (BMJ)*, reported antibacterial effects of black elderberry against pathogenic microbes that could cause bacterial super-infection in susceptible patients.

Finally, black elderberry appears to offer some proactive prevention against the common cold. A 2016 randomized controlled trial found that airline travelers supplemented with black elderberry syrup experienced significantly fewer, less severe, and shorter duration of common cold symptoms when compared with those taking placebo.

**Benefits:** Black elderberry may reduce the severity, duration, and complications of the flu. It may also play a role in the proactive prevention of the common cold.

**Dosing:** Black elderberry extract obtained from cultivar elderberries is naturally higher in flavonoids and active compounds. A daily dosage of 100 mg standardized extract (equivalent to 6,400 mg of berries) can be taken daily.

### Echinacea

Echinacea refers to a group of plant species, which includes *Echinacea purpurea*, *Echinacea angustifolia*, and *Echinacea pallida*. *E. purpurea* has been studied most extensively, but the various forms of Echinacea contain similar active compounds (such as echinacosides and alkylamides) and have similar therapeutic effects. Preparations of the root contain compounds that most directly support an acute immune response, and preparations of the aerial parts provide ongoing immune support.

There is some controversy over the efficacy of Echinacea for treating or preventing the common cold. A 2015 review, published in the *JAMA* and the *Cochrane Reviews*, evaluated 24 randomized clinical trials with 4,631 participants. The authors concluded that Echinacea products “slightly reduce the risk of getting a cold in healthy individuals” but that the evidence for Echinacea in treating colds is weak. The individual studies varied greatly because of different forms and preparations of Echinacea used.

Some evidence suggests that Echinacea is most beneficial for treating acute viral infections when combined with additional herbs. A 2016 study found an Echinacea combination product to be equally effective at reducing duration of illness as the antiviral medication oseltamivir and more effective at reducing flu complications. A combination of Echinacea, *Thuja occidentalis*, and *Baptisia tinctoria* has antibacterial efficacy against bronchial infections and is commonly used in Europe for acute upper respiratory infections.

**Benefits:** Echinacea may reduce the risk of the common cold. When used in combination products, it may reduce the severity, duration, and complications of the flu.

**Dosing:** A combination of 1,000 mg Echinacea extract with other immune-supporting herbs can be taken daily for acute immune support.



## Guaifenesin

Guaifenesin (glycerol guaiacolate) is a synthetic version of an active compound that naturally occurs in the resin of the Guaiac tree (*Guaiacum officinale*). Guaifenesin was FDA-approved in 1952 as an over-the-counter medication for its expectorant and antitussive properties.

Efficacy studies of guaifenesin for the treatment of cough and upper respiratory congestion have been mixed. A 2014 Cochrane review identified 3 clinical trials of guaifenesin for acute cough, only 1 of which reported significant benefit of guaifenesin over placebo. The study that reported a significant result showed that 75% of patients receiving guaifenesin found the intervention to be “helpful,” compared with only 31% of patients receiving placebo. In addition, a 2012 study of 378 participants with acute upper respiratory tract infections found that patient-reported outcomes in a daily cough and phlegm diary strongly favored guaifenesin over placebo at day 4 of the intervention.

**Benefits:** Guaifenesin may reduce the severity of cough and phlegm symptoms in patients with acute upper respiratory tract infections.

**Dosing:** 200-400 mg guaifenesin taken every 4 hours, up to a maximum of 2,400 mg per 24-hour period.

## Ivy Leaf Extract

English Ivy (*Hedera helix*) leaf extract has historically been used as a remedy for productive coughs and bronchial inflammation. Studies have shown ivy leaf extract to have expectorant, antitussive, anti-inflammatory, and antiviral properties.

A 2015 systematic review identified 10 clinical trials that evaluated the efficacy of ivy leaf extract in patients with bronchitis, asthma, or chronic obstructive pulmonary disease. Most studies demonstrated antitussive and mucolytic effects of ivy leaf extract that matched or exceeded other common therapies, such as ambroxol or n-acetyl cysteine (NAC). A 2011 meta-analysis also identified 10 eligible studies, including 17,463 patients with acute upper respiratory tract infections. Despite a lack of rigorous methodology, all 10 of the studies found ivy leaf to reduce symptoms.

Ivy leaf extract contains essential oils and flavonoids, but it is the saponins that are responsible for its soothing effect on bronchial passages. One specific saponin, hederacoside C, prevents the internalization of  $\beta_2$ -adrenergic receptors on bronchial and alveolar cells,

resulting in bronchodilation and increased secretion of surfactant. Preparation methods that standardize hederacoside C are therefore required to provide the pharmaceutical effect of ivy leaf extract. The most extensively researched preparation of ivy leaf extract in clinical trials has a dry extract ratio of 5-7.5 to 1.

**Benefits:** English ivy (*Hedera helix*) leaf extract has been shown to reduce symptom severity of upper respiratory infections. It is particularly indicated in those with bronchial irritation or a productive cough.

**Dosing:** English ivy (*Hedera helix*) leaf extract is dosed in drops or syrup. A standardized preparation providing 25 mg of dried ivy leaf extract and 9 mg of hederacoside C per serving can be taken as needed, 2-6 times per day, during an acute upper respiratory infection.

## Lactoferrin and Probiotics

Lactoferrin is an iron-binding protein present in milk, secreted in the gastrointestinal tract, and produced by white blood cells at the site of infected tissue. *In vitro* studies show that lactoferrin inhibits viral attachment to targeted cells. Lactoferrin also promotes a systemic immune response, enhancing NK cell activity and TH1 cytokine activity. A 2014 review article identified 2 clinical trials demonstrating benefit of lactoferrin for reducing the risk of the common cold in humans and 1 animal study suggesting potential protective effects against the influenza A virus. There are no studies to date evaluating lactoferrin for the flu in humans.

Probiotic bacteria, including *Lactobacillus acidophilus*, *L. rhamnosus*, and *Bifidobacterium longum*, support a healthy microbial balance in the digestive system and modulate immune function. A 2014 pilot study of school children in Japan found that children who were supplemented with a daily probiotic drink experienced a significantly lower incidence of the flu than children who did not. A 2009 study, also in school children, demonstrated that 6-months of probiotic supplementation



reduced the risk of fever, runny nose, cough, and days of missed school when compared with placebo.

In order for probiotics to be effective as dietary supplements, they must be delivered as active cultures that are protected from heat, moisture, oxygen, and stomach acid.

**Benefits:** Probiotics and lactoferrin may support immune function and provide proactive prevention against viral respiratory infections.

**Dosing:** Probiotics can be taken at a dosage of 1 billion colony-forming units (CFUs) per day with lactoferrin for ongoing immune support.

### Pelargonium

*Pelargonium sidoides* is a native plant of South Africa. Extracts of *P. sidoides* contain polyphenols and other compounds that increase phagocytosis, stimulate ciliary activity, and have mucolytic effects. An aqueous extract of the root, diluted to a 1X homeopathic concentration (EPs 7630) has been extensively studied for the treatment of acute respiratory tract infections.

A 2013 Cochrane review identified 8 randomized controlled trials comparing *P. sidoides* to placebo or any other treatment for acute respiratory infections: 3 trials showed significant benefit for acute bronchitis in adults;

3 showed significant benefit for acute bronchitis in children; 1 showed benefit for sinusitis; and 1 showed benefit for the common cold. A 2008 meta-analysis evaluated clinical trials of the EPs 7630 and reported 6 out of 6 clinical trials to show benefit of the extract in treating acute bronchitis. Numerous studies have shown benefit of *P. sidoides* for the common cold, with a 2007 randomized controlled trial demonstrating superiority of the EPs 7630 extract to placebo for reducing symptom severity and duration of cold symptoms.

**Benefits:** *P. sidoides* extract may reduce the severity and duration of symptoms in the common cold and other acute respiratory infections.

**Dosing:** *P. sidoides* 1X (EPs 7630) can be dosed as drops or as syrup. Approximately 100 mg of active ingredient can be taken 3 times daily during acute infection.

### Vitamin D<sub>3</sub>

Vitamin D insufficiency is common in the general population, particularly in the elderly, and peaks during the winter months. Researchers have proposed that vitamin D insufficiency may be one mechanism to explain the seasonality of the common cold and flu.

Vitamin D is considered an immune modulator. It triggers macrophage proliferation and improves phagocytic

## Intervention Expectations of Natural Therapies

Intervention	Proactive Prevention	Reduce Symptom Severity	Decrease Duration of Illness
Black Elderberry			
Echinacea			
Guaifenesin			
Ivy Leaf Extract			
Lactoferrin and Probiotics			
Pelargonium			
Vitamin D			

potential, helping the innate immune response halt replication of infected cells. Despite the stimulatory effect on macrophage activity, however, vitamin D also prevents the excessive production of cytokines by macrophages. This is important because high levels of cytokine production correlate with increased symptom severity and even death from the flu.

A 2016 randomized controlled trial compared the effects of high-dose vitamin D (100,000 IU vitamin D<sub>3</sub> per month) to low-dose vitamin D (12,000 IU vitamin D<sub>3</sub> per month) in Colorado long-term care residents aged 60 and older. Over a 12-month period, those who received the high-dose vitamin D experienced fewer respiratory tract infections than those who received the lower dose.

Three meta-analyses, published between 2013 and 2017, evaluated the association between vitamin D and the risk of the common cold and flu. One of these detected a non-significant 6% risk reduction for respiratory tract infections with vitamin D<sub>3</sub> supplementation. The other 2, published in *PlosOne* and *BMJ*, detected statistically significant risk reductions with vitamin D<sub>3</sub> supplementation. The average effective dosage of vitamin D<sub>3</sub> was 1,600 IU per day, with daily dosing showing greater benefit than monthly bolus dosing.

**Benefits:** Vitamin D offers the greatest benefit for proactive prevention of respiratory infections. Because of its ability to modulate cytokine release from macrophages, vitamin D may also lessen the severity of flu symptoms if supplemented throughout the cold and flu season.

**Dosing:** The Recommended Dietary Allowance (RDA) of vitamin D<sub>3</sub> is 600 IU, but dosages of 1,000-5,000 IU per day may be required to maintain adequate serum levels through the winter months.

## Immune-Enhancing Lifestyle

Herbal and nutritional supplements are not the only way to protect against the common cold and flu. Proactive prevention relies on healthy immune function, and healthy immune function relies on a balanced lifestyle. Public health recommendations for lifestyle habits can serve as a guide, with individualization as needed.

Smoking cigarettes puts patients at risk for upper respiratory infections and can worsen symptoms when sick. Excessive alcohol consumption can also compromise immunity. The US Dietary Guidelines recommend women drink no more than 1 drink per day and men drink no more than 2.

Moderate and routine exercise has a beneficial effect on immune function, but intense or prolonged bouts of exercise have the opposite effect. The American College of Sports Medicine and the CDC recommend at least 2.5 hours per week of moderate-to-intense exercise, which equates to 30 minutes per day on 5 days per week.

Sleep and stress also influence immune function. The National Institutes of Health recommends that children sleep 10 hours per night and adults sleep 7-8 hours per night. Encouraging patients to participate in activities they enjoy, to nurture healthy relationships, to stay positive, and to laugh will help them reduce the physiologic impact of stress on immune health.

Finally, healthy dietary habits go a long way to strengthen immunity against the common cold and flu. The US Dietary Guidelines recommend adults eat 5-9 servings of fruits and vegetables per day. Unlike exercise, which is best in moderation, more fruits and vegetables provide more benefit. Green leafy vegetables, cruciferous vegetables, mushrooms, dark berries, garlic, onions, ginger, and fermented foods provide antioxidants, micronutrients, and probiotics to support strong immune function.

## Conclusion

Clinicians, patients, and consumers put their trust in herbal and nutritional supplements to enhance immune function through the cold and flu season, but not all remedies are supported by scientific studies.

For the proactive prevention of acute viral infections, there is evidence to support the use of black elderberry, Echinacea, lactoferrin, probiotics, and vitamin D.

For the reduction of symptom severity or duration of illness, there is evidence to support the use of black elderberry, Echinacea combinations, ivy leaf extract, guaifenesin, and Pelargonium extract. Black elderberry is effective for reducing the symptoms and duration of influenza, and Pelargonium extract (EPs 7630) is a well-studied intervention for the common cold. Echinacea is most effective when combined with additional herbal ingredients. Ivy leaf extract is indicated when there is a productive cough, and guaifenesin acts as an expectorant.

Nutritional and herbal interventions are most effective when combined with a healthy lifestyle to support innate and adaptive immune responses through the cold and flu season.

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