

Cold & Flu – Natural Medicine Review
MPTCQ Hot Topic, March 2018

BACKGROUNDColds

- Common – especially in children
- Symptoms generally mild
- Caused by > 200 different viruses, but rhinovirus accounts for 30-50% of all colds
- Spread by physical contact with the virus & via airborne transmission
- Present all year, but peaks April-May & September

Influenza

- Less common, but more serious
- Caused by 3 types of viruses – influenza A, B & C
- Spread by physical contact with the virus & via airborne transmission
- Seasonal – usually November-May in northern hemisphere
- Viral proteins can change each year, making them appear “new” to the immune system – makes vaccine development difficult

Symptoms of Cold and Flu		
Symptom	Common Cold	Influenza
Onset	more gradual	abrupt
Headache	mild, uncommon	severe, common
Fever	uncommon or 0.5° C (1° F) increase	common 37.7 to 40° C (100 to 104° F)
Myalgia, arthralgia	uncommon	common
Malaise	mild	severe
Fatigue, weakness	very mild, short duration	common, lasts 2 to 3 weeks
Cough (dry)	mild to moderate	common, severe
Chest discomfort	mild to moderate	common, severe
Anorexia	uncommon	common
Nasal congestion	common	occasional
Sneezing	common	occasional
Sore throat	common	occasional

Commonly Used Natural Medicines for Colds and Influenza

- **Antivirals**

- Bee propolis
- Elderberry (*Sambucus nigra*)
- Garlic (*Allium sativum*)
- Zinc

- **Immunomodulators**

- American ginseng (*Panax quinquefolius*)
- Andrographis (*Andrographis paniculata*)
- Astragalus (*Astragalus membranaceus*)
- Bee propolis
- Bifidobacteria
- Boneset (*Eupatorium perfoliatum*)
- Echinacea (*Echinacea angustifolia*, *Echinacea pallida*, *Echinacea purpurea*)
- Elderberry (*Sambucus nigra*)
- Essential Fatty Acids
 - Alpha-linolenic acid
 - Linoleic acid
- Garlic (*Allium sativum*)
- Goldenseal (*Hydrastis canadensis*)
- Lactobacillus rhamnosus GG
- Larch arabinogalactan (*Larix occidentalis*)
- Oscillocoquinum
- Panax ginseng
- Pau d'arco (*Tabebuia impetiginosa*)
- Siberian ginseng (*Eleutherococcus senticosus*)
- Umckaloabo (*Pelargonium sidoides*)
- Vitamin C
- Vitamin E
- Wild indigo (*Baptisia tinctoria*)
- Zinc

PREVENTION

Vaccines

- Cold vaccine(?)
 - Development is unlikely
 - Too many different types of rhinovirus
- Flu vaccine
 - Already in production, effective
 - Prevents severe disease, hospitalization, and death
 - CDC encourages vaccination for EVERYONE over 6 months of age, except for those with contraindications

- Most people should get vaccine in October-November
 - Takes 2 weeks for vaccine to provide max protection
 - Lasts for ~ 6 months
 - No evidence that > 1 dose of flu shot is warranted in adults (no added benefit)
 - Children < 10 yrs who are receiving flu shot for the first time should receive booster 1 month later
- *FluMist* = intraNASAL vaccine
 - Contains live attenuated flu viruses
 - NOT recommended for people < 2 and > 49, pregnant women, or patients with chronic disease
 - Can't be given to immunocompromised patients
- 2017-2018 vaccine effectiveness (VE) rates
 - Early and widespread flu activity this year
 - Vaccine was initially estimated to be less effective than usual, but those reports were premature
 - 25% VE vs H3N2 (predominant strain)
 - Higher VE in children (6 mo-8 yrs)
 - Higher VE for H1N1 strain (67%) and B viruses (42%)

Antivirals

- Used as alternatives to flu shot for patients who can't get a flu vaccine (e.g. immunocompromised)
- Must be used throughout flu season
- Zanamivir (*Relenza*), oseltamivir (*Tamiflu*), and peramivir (*Rapivab*)
 - Neuraminidase inhibitors
 - Better tolerated vs older antivirals
 - Prevent viruses from penetrating the surface of healthy cells, inhibit release of viruses from infected cells
 - Zanamivir & oseltamivir → equally effective, effective against both influenza A & B
 - Peramivir → administered IV

Immunomodulators

- Intent is to "boost" or "support" the immune system
- WARNING: Patients with autoimmune disease (e.g. RA, Lupus, psoriasis) should avoid taking immunostimulants

Andrographis

- "Indian echinacea"
- Used to prevent both colds and flu
- Thought to have immunostimulant properties
- Preliminary evidence suggests taking andrographis reduces risk of catching a cold by 50% after two months of continuous use
 - But how long benefit lasts is not known (or if it is safe for continuous, long-term use)
- Bottom Line: Promising, but too soon to recommend

Astragalus

- Chinese herb
- Thought to prevent colds and flu
- Some evidence that it can stimulate lymphocyte production, but clinical significance unclear
- Bottom Line: Theoretical benefit, but no clear evidence – do not recommend

Echinacea

- Widely used to prevent URIs
- MOA: stimulates the immune system, causing macrophages to produce tumor necrosis factor, interleukin-1, and beta-interferon
- Studies have been mixed
 - Many have shown it to be ineffective for cold prevention, but two meta-analyses suggested that taking echinacea prophylactically significantly decreases the odds of developing the common cold (45-58%)
- WARNING: Patients with ragweed allergies should NOT to use Echinacea
- Bottom Line: Promising, but more evidence is needed

Garlic

- Might have immunostimulant activity and/or antiviral activity
- Might reduce the chance of catching a cold: in one small study, patients taking a garlic supplement daily between November & February had 1 fewer cold vs patients taking PBO
- WARNINGS:
 - Potential drug interactions
 - Warfarin: Might increase INR → potentially increase risk for bleeding
 - P450 3A4 substrates: 3A4 inducer, though some exceptions have been noted (e.g. docetaxel, rifampin)
 - HIV medications: Avoid combining allicin-containing garlic supplements with NNRTIs (e.g. efavirenz, *Sustiva*) and protease inhibitors (e.g. saquinavir, *Invirase*)
 - Dose-related adverse effects
 - Bad breath, body odor
- Bottom Line: Promising, but more evidence is needed before it can be recommended; watch for DDIs & side effects

Panax ginseng

- “Asian ginseng”
- Might have immunostimulant effects
- Might protect against colds + improve response to the flu vaccine?
 - Taking *Panax ginseng* 100 mg/day starting 4 weeks prior to influenza vaccination and continuing for 8 weeks after seems to reduce the risk of contracting both the cold and flu
 - MOA: increase natural killer cell activity and the antibody response to vaccination?
- Bottom Line: Still too soon to recommend *Panax ginseng* for this use, but studies are promising

American ginseng

- Some evidence suggests that taking a specific American ginseng extract called CVT-E002 (*Cold fx*, Afexa Life Sciences, Canada) 200 mg twice daily over a 3-4 month period during influenza season might decrease the risk of developing symptoms of a URI in adults aged 18+
 - Might reduce the risk of getting repeat colds in same season
 - When URIs do occur, seems to reduce the symptom severity & duration
- Note: these findings only pertain to this particular extract
- Bottom Line: Promising, but still too soon to recommend

Probiotics

- Gaining interest for reducing the risk of URIs
- Research suggests that milk fortified with a specific strain of probiotic, **Lactobacillus rhamnosus** GG (*Culturelle Every Day Health*) seems to modestly reduce the incidence of URIs in young children in day care
- Research also shows children ages 3-5 years who attend day care centers have significantly fewer influenza-like respiratory symptoms when given milk containing a combination of **Lactobacillus acidophilus** + **Bifidobacterium animalis** (*HOWARU Protect*, Danisco).
 - 45% lower risk of experiencing fever, cough, or rhinorrhea (vs PBO)
 - reduced duration of symptoms by 2 days
 - significant reduction in antibiotic use
- Bottom Line: Evidence is still fairly preliminary (and mainly in kids), but looks promising and safe for most people

Linoleic acid & alpha-linolenic acid

- Essential fatty acids
- Might reduce respiratory infections in children
- MOA: Beneficial effect on immune function?
- Bottom Line: Evidence is too preliminary to recommend

Vitamin E

- Used for preventing respiratory infections, primarily in the elderly
- Might increase antibody response to vaccination, but taking vitamin E supplements does not seem to lower the risk of respiratory infections
- Bottom Line: Not enough evidence to support use

Zinc

- Inhibits rhinovirus replication *in vitro*, but there's no evidence this happens *in vivo*
- Studies have shown:
 - Might increase cell-mediated immune response in elderly people, but no reliable evidence that zinc supplements can PREVENT a cold
 - Does not prevent the flu in vaccinated, institutionalized elderly patients
 - A combination of zinc + selenium might improve antibody response to the flu vaccine and/or reduce the chance of URI in elderly patients with nutrient deficiency
- Bottom Line: Not enough evidence to support use in most people (exception: elderly w/ nutrient deficiency?)

Vitamin C

- May increase T-lymphocyte activity, phagocyte function, leukocyte mobility, and possibly antibody and interferon production
 - But most evidence suggests that even in doses up to 1 gram/day, vitamin C does NOT prevent colds
 - Even increasing DIETARY vitamin C intake does not seem to affect the risk of getting a cold
- Bottom Line: Despite popularity, no evidence to support use

Combo product: *Airborne*

- "Developed by a school teacher who was sick of catching colds in class"
- Contains: vitamin C, vitamin E, vitamin A, zinc, echinacea, other ingredients
- No reliable evidence that it can prevent or treat a cold
- Bottom Line: No evidence to support use

TREATMENT

Significant overlap with products mentioned above (i.e. used for both prevention and treatment).

Antivirals

NOT effective for common cold → only influenza

- Amantadine & rimantadine
 - Used to treat influenza A
 - Viral resistance can develop in 25-35% of patients
- Oseltamivir & zanamivir
 - Effective for both influenza A & B
 - If started within 48 hours of onset of symptoms → duration cut by 1-2 days
 - Decreases the risk of flu complications (e.g. pneumonia, otitis media)
 - Significant viral resistance has not been reported

Immunomodulators

Andrographis extract + **Siberian ginseng** (*Kan Jang*, Swedish Herbal Institute)

- May significantly improve symptoms of cold when started within 72 hours of symptom onset
- Usually takes 4-5 days of treatment before maximal symptom relief noted
- ONLY this specific extract and combination product (*Kan Jang*) has been studied; not known if other preparations are effective
- Bottom Line: May be effective but must use *Kan Jang* product and needs to be started soon after symptom onset

Bee propolis

- May have antimicrobial and antiviral effects
- Might decrease the duration of cold symptoms by 2.5x compared w/ PBO in patients with rhinovirus infection
- Also: **honey** → shown to have antimicrobial properties
- Bottom Line: Not enough evidence to support use

Echinacea

- Used commonly for prevention
- Appears to have immunostimulant & anti-inflammatory effects
- Studies have been mixed: some studies show modest improvement in symptom duration and severity (10-30%), but others show no benefit
 - Due to lack of standardization in studies?
- Best evidence w/ preparations of the *Echinacea purpurea* species
- WARNING: Patients with ragweed allergies should NOT to use Echinacea
- Bottom Line: Evidence is mixed – if patient wants to use, recommend a product with *Echinacea purpurea* species

Elderberry

- Has both antiviral and immunomodulating effects
 - Increases production of inflammatory cytokines (e.g. interleukins, TNF)
 - Prevents viral attachment to cells
 - Active against both influenza A & B
- A standardized elderberry fruit extract in syrup formulation (*Sambucol*, Nature's Way), 4 tablespoons daily x 3 days, was shown to:
 - Shorten the duration of symptoms by ~56%
 - Reduce severity of symptoms (e.g. fever, myalgia)
- Lozenge formulation (*ViraBLOC*, Herbal Science), 175 mg QID, reduces symptoms after 2 days (vs PBO)
- Bottom Line: Evidence is promising, but better evidence w/ Rx antiviral drugs (don't rely on it for high-risk patients)

Oscillocochinum

- Homeopathic dilution of duck liver and heart extract
 - Note: based on principles of homeopathy, most products are so diluted they contain little-to-no active ingredient
- No proof that it prevents or treats the flu
- Bottom Line: No evidence to support use (and may not even contain the “active” ingredient)

Umckaloabo

- “African Geranium”
- Has antimicrobial and immunostimulatory effects
- One study: Adults taking 1.5 mL extract TID x 10 days have reduced cold symptoms and complete resolution after 10 days
- Strongest evidence is in treatment of other respiratory infections (e.g. bronchitis, tonsillopharyngitis)
- Generally well-tolerated
- Bottom Line: Likely safe, evidence is limited but promising

Vitamin C

- Commonly used for cold treatment/prevention, but evidence is mixed
- Some studies suggest that taking high doses of vitamin C orally might decrease the duration of cold symptoms by 1-1.5 days, but other studies have found no effect (doses up to 3 g daily)
- More effective for treating cold symptoms in children (vs adults)?

- Dose-dependent response
 - 2+ g/day seem to work better than 1 g/day
- Downside = High doses used for treatment of colds come with more side effects (e.g. diarrhea)
- Bottom Line: Evidence is mixed – likely more effective for kids vs adults, doses required may cause side effects, clinically significant?

Zinc

- Commonly used for cold treatment/prevention, but evidence is mixed
- Lozenges
 - Some studies suggest that zinc lozenges (9-24 mg elemental zinc/dose) started within 24-48 hours of the onset of cold symptoms reduce severity and duration of colds → other studies show no effect
 - Requires frequent dosing; every 2-3 hrs while awake
 - Side effects: dry or astringent feeling in the mouth
- Nasal Spray/Gel
 - e.g. *Zicam Cold Remedy Nasal Gel*
 - Anosmia (rare, permanent)
 - *Zicam* nasal spray removed from US market in 2009 due to 130+ reports
- Bottom Line: Evidence is mixed, lozenges require frequent dosing, concern re: side effects with nasal spray/gel

Other supplements: **goldenseal**, **pau d'arco**, **astragalus**, **larch arabinogalactan**, **eucalyptus**, **boneset**, **wild indigo**, and **Siberian ginseng**.

- Marketed as "immune system supporters"
- Used alone or in combination with other natural products, such as echinacea
- Bottom Line: Not enough evidence to support use

Saline nasal irrigation

- Applied with spray bottle or Neti Pot
- Often recommended as a benign cold treatment
- Studies show: isotonic saline nasal irrigation significantly reduces symptoms of cold (rhinitis, sore throat, cough, nasal obstruction/secretion) in children and adults
- Medication-sparing effect (reduces use of antipyretics, decongestants, mucolytics, and anti-infectives)
- BUT, some research has shown no significant benefit
- Counseling points:
 - Use boiled, bottled, or distilled water
 - Wash pot w/ hot soapy water after every use; don't share pots
 - Rinse bottles changed monthly
- Bottom Line: Evidence is mixed, but when used appropriately it is considered safe and might help

Teas

- Usually made with **elderflower**, **rose hip**, **goldenseal**, **chamomile**, **peppermint**, **slippery elm**, **ginger**, **Mormon tea**, **linden flowers**, **licorice**, **meadowsweet**, others
- Bottom Line: The hot liquid may be soothing, but there's no reliable evidence for efficacy

SUMMARY

Conventional medicine lacking for cold & flu prevention/treatment → many people turn to natural medicines instead.

Prevention:

- Despite their popularity, echinacea, vitamin C, and zinc don't prevent colds.
- Some evidence suggests Panax qinseng might improve response to influenza immunization.

Treatment:

- Andrographis seems to reduce the duration and severity of cold symptoms.
- Echinacea also seems to reduce the duration and severity of cold symptoms, but evidence has been contradictory.
- Elderberry seems to lessen the severity of flu symptoms, but there's still better evidence for conventional medicines so don't rely on this in high-risk patients.
- Saline nasal irrigation is gentle & safe if used appropriately; can help with symptom management.
- Vitamin C is controversial; high doses might reduce the duration of cold symptoms but might not be clinically significant.
- Zinc lozenges might reduce the severity and duration of colds but must be started quickly, dosed frequently, and nasal spray should not be used due to risk of anosmia.

Recommendation Chart for Natural Medicines Used for Colds and Flu * Colds and Influenza Treatment						
Safety \ Effective	Likely Safe	Possibly Safe	Insufficient Evidence	Possibly Unsafe	Likely Unsafe	Unsafe
Effective						
Likely Effective						
Possibly Effective	- Andrographis - Echinacea - Vitamin C - Zinc (lozenges)	- Elderberry		- Zinc (nasal spray)		
Insufficient Evidence	- Saline nasal irrigation - Umckaloabo	- Astragalus - Bee propolis - Goldenseal - Larch arabinogalactan - Oscillacoccinum - Siberian ginseng		- Boneset - Pau d'arco		- Wild indigo
Possibly Ineffective						
Likely Ineffective						
Ineffective						

Recommendation Chart for Natural Medicines Used for Colds and Influenza Prevention *						
Safety \ Effective	Likely Safe	Possibly Safe	Insufficient Evidence	Possibly Unsafe	Likely Unsafe	Unsafe
Effective						
Likely Effective						
Possibly Effective	- American ginseng - Bifidobacteria - Echinacea (colds)					
Insufficient Evidence	- Alpha-linolenic acid - Andrographis - Echinacea (flu) - Garlic - Lactobacillus GG	- Astragalus - Linoleic acid (from flaxseed oil) - Panax ginseng				
Possibly Ineffective	- Vitamin C - Vitamin E - Zinc					
Likely Ineffective						
Ineffective						

KEY:
Consider recommending this product.
Don't recommend using this product.
Recommend against using this product.

*NOTE: These proposed recommendations are based solely on the Safety and Effectiveness Ratings contained in *Natural Medicines Comprehensive Database*. This assumes use of high-quality, uncontaminated products, and the use of typical doses. Keep in mind that some products are never appropriate for some patients due to concomitant disease states, potential drug interactions, or other clinical factors. Use your clinical judgment before recommending any product.

REFERENCES

1. "Natural Medicines in the Clinical Management of Colds and Flu." *Pharmacist's Letter*. Online Continuing Education and Webinars, Volume 15, No. 109. Self-Study Course #150109. Last accessed 3/28/18.
2. Natural Medicines Comprehensive Database. Last accessed 3/28/18.