Complementary and alternative medicine for prevention and treatment of the common cold

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Abstract

Objective To review the evidence supporting complementary and alternative medicine approaches to treatment and prevention of the common cold in adults.

Quality of Evidence MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from January 1966 to September 2009 combining the key words *common cold* or *influenza* with *echinacea*, *garlic, ginseng, probiotics, vitamin C*, and *zinc*. Clinical trials and prospective studies were included.

Main Message For prevention, vitamin C demonstrated benefit in a large meta-analysis, with possibly increased benefit in patients subjected to cold stress. There is inconsistent evidence for Asian ginseng (Panax ginseng) and North American ginseng (Panax quinquefolius). Allicin was highly effective in 1 small trial. For treatment, *Echinacea purpurea* is the most consistently useful variety; it was effective in 5 of 6 trials. Zinc lozenges were effective in 5 of 9 trials, likely owing to dose and formulation issues. Overall, the evidence suggests no benefit from probiotics for prevention or treatment of the common cold.

Conclusion Vitamin C can be recommended to Canadian patients for prevention of the common cold. There is moderate evidence supporting the use of *Echinacea purpurea* and zinc lozenges for treatment. Ginseng and allicin warrant further research.

Résumé

Objectif Examiner les données en faveur du recours aux médecines complémentaires et alternatives pour traiter et prévenir le rhume banal chez l'adulte.

Qualité des preuves On a consulté MEDLINE, EMBASE et la Cochrane Database of Systematic Reviews entre janvier 1966 et septembre 2009, en combinant les rubriques common cold ou influenza avec les rubriques Echinacea, garlic, ginseng, probiotics, vitamin C et zinc. Des essais cliniques et des études prospectives ont été inclus.

Principal message Pour ce qui est de la prévention, la vitamine C s'est avérée bénéfique dans une grande méta-analyse, avec une protection possiblement meilleure chez les sujets exposés au froid. Pour le ginseng asiatique (Panax ginseng) et le ginseng nord-américain (Panax quinquefolius), les données sont contradictoires. L'allicine était très efficace dans un petit essai. Pour le traitement, c'est l'Echinacea purpurea qui est le plus régulièrement utile, s'étant montré efficace dans 5 essais sur 6. Les losanges de zinc étaient efficaces dans 5 essais sur 9, possiblement à cause de différences de doses et de préparation. Dans l'ensemble, les données suggèrent que les probiotiques ne sont pas utiles pour prévenir ou traiter le rhume banal.

Conclusion On peut recommander la vitamine C aux patients canadiens pour prévenir le rhume banal. Il existe certaines données en faveur de l'utilisation de l'Echinacea purpurea et des losanges de zinc pour le traitement. Le ginseng et l'allicine devront être étudiées davantage.

KEY POINTS For prevention, the most consistent evidence supports use of at least 1 g of vitamin C daily, which decreased symptom duration by 8% in adults and 18% in children in several trials and which might be even more effective during Canadian winters. Use of ginseng and allicin could be considered; both show promise but larger trials are needed. Evidence from patients subjected to cold stress reinforces the importance of dressing warmly. For treatment, *Echinacea purpurea* taken at the first signs of a cold might reduce duration and severity of symptoms. Zinc lozenges might also be effective. Published studies are difficult to interpret in both cases because of differences in dose and formulation.

POINTS DE REPÈRE Pour ce qui est de la prévention, les preuves les plus solides obtenues dans plusieurs essais indiquent que la prise quotidienne d'au moins 1 g de vitamine C diminue la durée des symptômes de 8% chez l'adulte et de 18% chez l'enfant, et suggèrent que son efficacité pourrait être encore meilleure durant les hivers canadiens. Des résultats prometteurs permettent d'envisager l'usage du ginseng et de l'allicine, mais d'autres études seront nécessaires. Les données confirment l'importance d'être chaudement vêtu en cas d'exposition au froid. Pour ce qui est du traitement, la prise d'*Echinacée purpurea* aux premiers signes de rhume pourrait réduire la durée et la sévérité des symptômes. Les losanges de zinc pourraient aussi être efficaces. Dans ces deux derniers cas, les études publiées sont difficiles à interpréter en raison des différences de doses et de préparation.

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The common cold is seen frequently by family physicians. It is almost always a viral illness; while rhinoviruses cause 30% to 50% of colds throughout the year and 80% of colds during peak season, up to 200 other viruses have been implicated.1 On average, it affects adults 2 to 4 times per year.2

Symptoms include nasal congestion and discharge, sneezing, cough, sore throat, and fever.[3] While benign, they last for several days and cause 40% of all missed work days. Complications include sinusitis, otitis media and pneumonia, exacerbations of asthma and chronic obstructive pulmonary disease, and serious illness in immunocompromised patients. Influenza viruses cause 5% to 15% of acute respiratory infections, resulting in fever, headache, myalgia, and fatigue, and considerable overlap between influenza and the common cold can make accurate diagnosis difficult.[3]

Few effective treatments exist. Nonsteroidal anti-inflammatory drugs reduce pain symptoms but not the overall duration or severity of a cold,[4] and the antiviral drug oseltamivir only reduces symptom duration by 0.55 days in otherwise healthy adults.[5] There is no role for antibiotics in the treatment of the common cold. While vaccination of healthy adults prevents influenza, it only reduces incidence of acute respiratory infections by 16%, and work absenteeism by 0.13 days.[6]

Many patients use complementary and alternative medicine (CAM) therapies to treat the common cold. Canadians spend more than $1 billion per year on CAM therapies,[7] but few physicians are familiar with their efficacy or safety. Here we review the evidence for frequently used CAM therapies to help physicians advise patients about the use of such therapies in treating and preventing the common cold.

Quality of evidence

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched from January 1966 to August 2009. Key words used were *common cold* or *influenza* with *echinacea, garlic, ginseng, probiotics, vitamin C,* and *zinc*. The interventions were selected based on literature reviews and clinical experience. We identified clinical trials and other prospective studies, systematic reviews, and meta-analyses. Only trials evaluating single agents, mostly in healthy adults, were selected. Review articles and references were screened for additional trials. Each article was reviewed separately by both authors.

The main limitation of the methodology used is the exclusion of other potentially useful interventions. This paper is not meant to be comprehensive, but rather to review the evidence for interventions that are commonly seen in clinical practice.

Main findings

Relevant findings for each search term are briefly summarized in **Table 1**[8-37] and are detailed as follows:

Echinacea. Echinacea roots and flowers were used medicinally by First Nations peoples and became popular in Europe for infectious problems. In laboratory studies, they activate macrophages, increase phagocytosis, enhance cytokine production[38] and natural killer cell activity, and improve lymphocyte and monocyte cell counts[10] and antibody response.[39] Many active ingredients have been identified, but recent attention has focused on alkylamides, which bind to cannabinoid receptors and upregulate the transcription of tumour necrosis factor.[40]

Clinical trial results have been difficult to interpret because they have used different species and plant parts. A recent Cochrane systematic review of echinacea for treatment and prevention of the common cold[41] found more evidence for *Echinacea purpurea* than *Echinacea angustifolia* or *Echinacea pallida*, and more for aerial parts than roots. Given this, this review is limited to studies of *E purpurea*.

Treatment: Of the 11 trials identified that studied echinacea,[8-15,42-44] 6 trials evaluated *E purpurea* in 764 healthy adults with cold symptoms.[10-15] Symptom severity was reduced in 4 of 6 trials,[10-12,14] measured using total daily symptom scores and Jackson scores. Of the

Table 1. Complementary and alternative medicine therapies for the common cold

INTERVENTION	EVIDENCE FOR PREVENTION (LEVEL*)	EVIDENCE FOR TREATMENT (LEVEL*)
Echinacea purpurea	No evidence found in 2 RCTs (level IIa)[8,9]	Evidence found in 5 of 6 RCTs (level IIa)[10-15]
Zinc lozenges	No trials evaluate prevention	Evidence found in 5 of 9 RCTs (level IIa)[16-24]
Vitamin C	Evidence found in meta-analysis of 30 RCTs; more benefit in children and in adults under stress (level I)[25]	No evidence found in meta-analysis of 11 RCTs (level I)[25]
Ginseng	Inconsistent; evidence found in 2 of 4 RCTs (level IIb)[26-29]	No trials evaluate treatment
Garlic (allicin)	Evidence found in 1 RCT (level IIb)[30]	No trials evaluate treatment
Probiotics	No evidence found in 4 of 6 RCTs (level IIa)[31-36]	No trials evaluate treatment

RCT—randomized controlled trial.
*Levels of evidence indicated are taken from the Oxford Centre for Evidence-Based Medicine.[37]

4 trials that measured duration of symptoms,[12-15] 3 found significant reductions of 1.5,[12] 3,[14] and 4 days[13] ($P<.05$ for all). Only 1 study found no reduction in symptom severity or duration.[15]

The 6 trials used 5 distinct preparations: 3 tinctures[11,13-15] and 2 tablets derived from various extracts.[10,12] Three trials studied healthy adults,[11,14,15] while the other 3 studied adults with 2 or more colds in the previous year.[10,12,13] Different clinical scoring systems were also used. There is moderate evidence that *E purpurea* might be effective for treatment of the common cold, but issues surrounding dose and formulation require clarification before it can be recommended for routine use.

Prevention: Two trials evaluating *E purpurea* in cold prevention found no reduction in symptom duration or severity.[8,9]

Safety and use: A typical dose of echinacea is 2000 to 3000 mg of crude extract, 6 to 9 mL of pressed juice, or 0.75 to 1.5 mL of tincture per day. The most important concern is allergy; echinacea is a member of the Asteraceae family and can cause serious reactions in susceptible patients.[45] Reported side effects include gastrointestinal upset, headache, and rash.[39,46,47] No herb-drug interactions have been identified. Its safety in pregnancy or for long-term use is unknown. The theoretical risk of worsening autoimmune disease has not been reported but should be considered.[39]

Ginseng. *Panax* means "heal-all" in Greek. *Panax ginseng* (Asian ginseng) has been used in Chinese medicine for millennia, and is believed to be an "adaptogen," which enhances an individual's ability to resist mental and physical stress.[48] In animal and human studies, it has activated macrophages, natural killer cells, and lymphocytes, and increased cytokine and antibody production.[49,50] *Panax quinquefolius* (North American ginseng) contains a similar chemical profile and is used to make COLD-fX, an extract standardized to polysaccharides and oligosaccharides.

Treatment: There are no trials evaluating ginseng for treatment of the common cold.

Prevention: Our search identified 3 trials comprising 564 patients that evaluated *P quinquefolius* for prevention of the common cold[26-28]; all were funded by the manufacturer. These trials were also identified in a recent systematic review.[51] Unfortunately, none involved healthy adults. One summarized 2 separate studies of 89 and 109 nursing home patients[26]; another involved 44 elderly patients (older than 65 years of age)[27]; and a third examined 323 unvaccinated adults with more than 2 colds in the previous year.[31] All patients received 200 mg per day of COLD-fX or placebo for 2 to 4 months.

Poor and misleading reporting of data makes it difficult to draw conclusions from these studies. The nursing home studies reported fewer laboratory-confirmed infections, but found no reduction in the number of colds or in the duration or severity of symptoms.[26] The study of 44 elderly patients reported fewer days of cold symptoms but only in the last 2 months of the 4-month trial; the number of colds was not reduced.[27] The final study reported that healthy adults at risk who took COLD-fX experienced milder symptoms (Jackson score 77.5 vs 112.3, $P=.002$) for fewer days (10.8 vs 16.5 days, $P<.001$).[28]

Only 1 trial has studied *P ginseng*; 227 vaccinated healthy adults took 100 mg of an extract or placebo for 12 weeks. Those in the group taking ginseng suffered far fewer colds (15 vs 42, relative risk 0.35, $P<.001$).[29]

Safety and use: Reported side effects include headache, gastrointestinal upset, anxiety, and insomnia. Ginseng should be avoided during pregnancy and lactation because of potential teratogenicity and estrogenic effects.[52] Case reports have described potential herb-drug interactions with phenelzine (induction of mania from depression), warfarin (increased international normalized ratio), and alcohol (increased blood clearance).[53]

There is conflicting and unclear evidence that *P quinquefolius* prevents colds. Although it is chemically similar to *P ginseng*, 1 clinical trial of *P ginseng* yielded better results, and its long history of traditional use is reassuring. Larger ginseng trials are warranted.

Vitamin C. Albert Szent-Györgyi won the Nobel Prize for his discovery of vitamin C. Another Nobel laureate, Linus Pauling, popularized its use for disease prevention and longevity.[54] Vitamin C has antioxidant properties, regenerates glutathione, and might stimulate neutrophil and monocyte activity.[55]

Treatment: A Cochrane systematic review identified 7 treatment trials evaluating 3294 cold episodes.[25] One trial found that patients who took 8 g of vitamin C at the onset of symptoms had more "short colds" of less than a day than those who took 4 g (46% vs 39%, $P=.046$). All other trials found no benefit, even at similar doses.[25]

Prevention: The same review identified 30 prevention trials involving 11 350 subjects. Overall, there was a very slight decrease in the number of colds (odds ratio [OR] 0.96, 95% confidence interval [CI] 0.92 to 1.0) but not in cold severity. Symptom duration decreased by 8.0% in trials that used more than 1 g daily in adults, and decreased by 18% (95% CI 7% to 30%) when this dose was used in children. Assuming that the average cold lasts for 7 to 10 days, this represents 1.5 to 2.0 days shorter duration, which is clinically relevant.

More important, the reviewers identified a subgroup of 6 trials of 642 subjects exposed to severe stress in the form of subarctic cold or intense physical activity. In these trials, those taking vitamin C at doses of 200 to 2000 mg daily had half as many colds as those taking

placebo (OR 0.50, 95% CI 0.38 to 0.66). This seems very relevant to patients in many Canadian communities.

Safety and use: Vitamin C is considered safe in doses up to several grams per day. The only occasional side effect is gastrointestinal upset, and doses in excess of 10 g can cause diarrhea. No drug interactions are known.

Taking at least 1 g of vitamin C per day can be recommended for the prevention of colds based on good evidence of moderate reduction in symptom duration in adults and children. While it only reduces symptoms by 1 to 2 days, it is cheap, safe, and simple to use. It can also be recommended for use by athletes in intense training. Further research should explore the potential benefit in Canadians, who are subjected to cold winters.

Allicin. Allicin is an organosulfur compound found in garlic (*Allium sativum*), a food with known cardiovascular[56,57] and anticancer benefits.[58] Allicin is released when garlic is chopped or chewed, but is inactivated by cooking.[59] It has demonstrated antiviral properties in vitro against rhinovirus and several other strains.[60]

Treatment: There are no trials evaluating allicin for treatment of the common cold.

Prevention: One study of 146 healthy adults compared a high-dose allicin extract (180 mg daily) with placebo for 12 weeks during the winter months. The results were dramatic; the treatment group had 64% fewer colds (24 vs 65, $P<.001$), and symptom duration was reduced by 70% (1.52 vs 5.01 days, $P<.001$). Those in the treatment group were much less likely to develop more than 1 cold (2 vs 16 participants developed more than 1 cold).[30]

Safety and use: It should be emphasized that the allicin preparation used in this trial is unlike typical garlic preparations. It contained 180 mg of allicin; fresh garlic contains 5 to 9 mg per clove, and most extracts contain less than this. The only side-effect reported in the trial was malodorous belching. Little is known about the safety of high-dose allicin, but its use could be considered.

Probiotics. The health benefits of fermented milk were first proposed in the early 20th century. These benefits are due to the presence of probiotic bacteria, which appear to be useful in several gastrointestinal and immune-mediated disorders.[61] They interfere with toxin and cell binding sites, and improve mucosal barrier function, intestinal microflora, and gut-associated lymphoid tissue.[62,63]

Treatment: There are no trials evaluating probiotics for treatment of the common cold.

Prevention: Probiotics were evaluated in 6 randomized controlled trials[31-36] involving 1766 healthy adults. The number of colds was significantly reduced in only 1 of 6 trials,[36] symptom severity in 1 of 6,[31] and duration in 1 of 5 ($P=.045$).[31] Two of the negative trials involved atypical populations (military cadets[33] and marathon runners[32]), but even when these are excluded, the results are unimpressive. There was no clear relationship between response and dose (measured in colony-forming units) or strain in studies that were large enough to be adequately powered. In a recent systematic review, there appeared to be more benefit in children,[64] but this is beyond the scope of this review.

Despite their lack of efficacy and potential for harm, antibiotics are still prescribed to patients with the common cold. These drugs alter intestinal flora, which can lead to potentially harmful side effects and complications. We recommend that patients use probiotics whenever antibiotics are prescribed.

Zinc lozenges. Zinc is an essential mineral used in hundreds of biochemical pathways, and deficiency has long been associated with infection risk. Postulated mechanisms in the common cold include interfering with rhinovirus protein cleavage or capsid binding to intracellular adhesion molecule–1 in nasal epithelium,[65] and protecting plasma membranes from microbial toxins and complement.[55]

Treatment: Zinc was evaluated in 13 trials for treatment of the common cold in adults.[16-24,66-69] A nasal spray was compared with placebo in 4 trials,[16,67-69] and it reduced symptom duration and severity in only 2 of these.[68,69] Irritation by the nasal sprays limits their use; they also appear to yield lower concentrations in the nasopharynx.[70] Therefore, they are considered separately.

Zinc lozenges reduced symptom duration and severity in 5[16,18-21] of 9 trials.[16-24] The results are difficult to interpret for 2 reasons. The first is dose; 4 of 5 studies[16,18-20] that used higher doses of elemental zinc (13 to 23 mg per lozenge every 2 hours) found a 1.3- to 6.9-day reduction in symptom duration and reduced symptom severity. Negative trials using lower doses have been criticized.[71]

The second issue is bioavailability. Negative trials have been criticized for using formulations that included citric or tartaric acids,[70] sorbitol, or mannitol,[72] all of which bind to and inactivate elemental zinc. More positive trials used acetate or gluconate, which do not bind to zinc as tightly as orotate or citrate. The importance of these differences is unclear. These factors might explain the variable results seen in a meta-analysis of 8 randomized controlled trials (OR 0.52, 95% CI 0.25 to 1.2) for symptoms after 7 days.[71]

It appears that zinc might be effective for treatment of colds, but issues surrounding dose and bioavailability require clarification. Future studies should use higher doses and ensure that formulations do not contain agents that could bind to or otherwise interfere with elemental zinc.

Prevention: There are no trials evaluating zinc for prevention of the common cold.

Safety and use: Lozenges containing at least 13 mg of elemental zinc can be used every 2 hours at the first sign of a cold. Reported side effects include bitter taste, nausea, and decreased smell and taste.[73,74] Prolonged use of zinc (6 to 8 weeks) is not recommended, as it can lead to copper deficiency.

Conclusion

For prevention, the most consistent evidence supports the use of at least 1 g of vitamin C per day, which decreased symptom duration by 8% in adults and 18% in children in several trials and which might be even more effective during Canadian winters. Use of ginseng and allicin can be considered; both show promise but larger trials are needed. Evidence from patients subjected to cold stress reinforces the importance of dressing warmly.

For treatment, *E purpurea* might reduce duration and severity of symptoms when taken at the first signs of a cold. Zinc lozenges might also be effective. Published studies are difficult to interpret in both cases because of differences in dose and formulation. Once again, more trials are needed.

These simple, safe recommendations might improve outcomes for patients with the common cold. Of equal importance, they offer an alternative when advising patients whose viral infections do not require antibiotics.

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Contributors
Both authors contributed to the literature search and preparing the manuscript for submission.

Competing interests
None declared

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References

1. Mäkelä MJ, Puhakka T, Ruuskanen O, Leinonen M, Saikku P, Kimpimäki M, et al. Viruses and bacteria in the etiology of the common cold. *J Clin Microbiol* 1998;36(2):539-42.
2. Monto AS. Epidemiology of viral respiratory infections. *Am J Med* 2002;112(Suppl 6A):4S-12S.
3. Heikkinen T, Järvinen A. The common cold. *Lancet* 2003;361(9351):51-9.
4. Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the common cold. *Cochrane Database Syst Rev* 2009;(3):CD006362.
5. Burch J, Corbett M, Stock C, Nicholson K, Elliot AJ, Duffy S, et al. Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis. *Lancet Infect Dis* 2009;9(9):537-45. Epub 2009 Aug 7.
6. Jefferson TO, Rivetti D, Di Pietrantonj C, Rivetti A, Demicheli V. Vaccines for preventing influenza in healthy adults. *Cochrane Database Syst Rev* 2007;(2):CD001269.
7. Esmail N. *Complementary and alternative medicine in Canada: trends in use and public attitudes, 1997-2006.* Vancouver, BC: Public Policy Sources, The Fraser Institute; 2007.
8. Grimm W, Müller HH. A randomized controlled trial of the effect of fluid extract of Echinacea purpurea on the incidence and severity of colds and respiratory infections. *Am J Med* 1999;106(2):138-43.
9. Melchart D, Walther E, Linde K, Brandmaier R, Lersch C. Echinacea root extracts for the prevention of upper respiratory tract infections: a double-blind, placebo-controlled randomized trial. *Arch Fam Med* 1998;7(6):541-5.
10. Goel V, Lovlin R, Chang C, Slama JV, Barton R, Gahler R, et al. A proprietary extract from the echinacea plant (Echinacea purpurea) enhances systemic immune response during a common cold. *Phytother Res* 2005;19(8):689-94.
11. Brinkeborn RM, Shah DV, Degenring FH. Echinaforce and other echinacea fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine* 1999;6(1):1-6.
12. 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* 2004;29(1):75-83.
13. Hoheisel O, Sandberg M, Bertram S, Bulitta M, Schafer M. Echinagard treatment shortens the course of the common cold: a double-blind placebo-controlled clinical trial. *Eur J Clin Res* 1997;9:261-8.
14. Schulten B, Bulitta M, Ballering-Brühl B, Köster U, Schäfer M. Efficacy of Echinacea purpurea in patients with a common cold. A placebo-controlled, randomised, double-blind clinical trial. *Arzneimittelforschung* 2001;51(7):563-8.
15. Yale SH, Liu K. Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004;164(11):1237-41.
16. Eby GA, Davis DR, Halcomb WW. Reduction in duration of common colds by zinc gluconate lozenges in a double-blind study. *Antimicrob Agents Chemother* 1984;25(1):20-4.
17. Douglas RM, Miles HB, Moore BW, Ryan P, Pinnock CB. Failure of effervescent zinc acetate lozenges to alter the course of upper respiratory tract infections in Australian adults. *Antimicrob Agents Chemother* 1987;31(8):1263-5.
18. Godfrey JC, Conant Sloane B, Smith DS, Turco JH, Mercer N, Godfrey NJ. Zinc gluconate and the common cold: a controlled clinical study. *J Int Med Res* 1992;20(3):234-46.
19. Mossad SB, Macknin ML, Medendorp SV, Mason P. Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study. *Ann Intern Med* 1996;125(2):81-8.
20. Petrus EJ, Lawson KA, Bucci LR, Blum K. Randomized, double-masked, placebo-controlled clinical study of the effectiveness of zinc acetate lozenges on the common cold symptoms in allergy-tested subjects. *Curr Ther Res* 1998;59(9):595-607.
21. Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000;133(4):245-52.
22. Smith DS, Helzner EC, Nuttall CE Jr, Collins M, Rofman BA, Ginsberg D, et al. Failure of zinc gluconate in treatment of acute upper respiratory tract infections. *Antimicrob Agents Chemother* 1989;33(5):646-8.
23. Turner RB, Cetnarowski WE. Effect of treatment with zinc gluconate or zinc acetate on experimental and natural colds. *Clin Infect Dis* 2000;31(5):1202-8. Epub 2000 Nov 6.
24. Weismann K, Jakobsen JP, Weismann JE, Hammer UM, Nyholm SM, Hansen B, et al. Zinc gluconate lozenges for common cold. A double-blind clinical trial. *Dan Med Bull* 1990;37(3):279-81.
25. Douglas RM, Hemilä H, Chalker E, Treacy B. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev* 2007;(3):CD000980.
26. McElhaney 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* 2004;52(1):13-9. Erratum in: *J Am Geriatr Soc* 2004;52(5):following 856.
27. McElhaney 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* 2006;12(2):153-7.
28. 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* 2005;173(9):1043-8.
29. Scaglione F, Cattaneo G, Alessandria M, Cogo R. Efficacy and safety of the standardised Ginseng extract G115 for potentiating vaccination against the influenza syndrome and protection against the common cold [corrected]. *Drugs Exp Clin Res* 1996;22(2):65-72. Erratum in: *Drugs Exp Clin Res* 1996;22(6):338.
30. Josling P. Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. *Adv Ther* 2001;18(4):189-93.
31. De Vrese M, Winkler P, Rautenberg P, Harder T, Noah C, Laue C, et al. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. *Clin Nutr* 2005;24(4):481-91. Epub 2005 Apr 21.
32. Kekkonen RA, Vasankari TJ, Vuorimaa T, Haahtela T, Julkunen I, Korpela R. The effect of probiotics on respiratory infections and gastrointestinal symptoms during training in marathon runners. *Int J Sport Nutr Exerc Metab* 2007;17(4):352-63.
33. Tiollier E, Chennaoui M, Gomez-Merino D, Drogou C, Filaire E, Guezennec CY. Effect of a probiotics supplementation on respiratory infections and immune and hormonal parameters during intense military training. *Mil Med* 2007;172(9):1006-11.

34. Tubelius P, Stan V, Zachrisson A. Increasing work-place healthiness with the probiotic Lactobacillus reuteri: a randomised, double-blind placebo-controlled study. *Environ Health* 2005;4:25.
35. Turchet P, Laurenzano M, Auboiron S, Antoine JM. Effect of fermented milk containing the probiotic Lactobacillus casei DN-114001 on winter infections in free-living elderly subjects: a randomised, controlled pilot study. *J Nutr Health Aging* 2003;7(2):75-7.
36. Winkler P, de Vrese M, Laue C, Schrezenmeir J. Effect of a dietary supplement containing probiotic bacteria plus vitamins and minerals on common cold infections and cellular immune parameters. *Int J Clin Pharmacol Ther* 2005;43(7):318-26.
37. Oxford Centre for Evidence-Based Medicine [website]. *Levels of evidence.* Oxford, UK: Oxford Centre for Evidence-Based Medicine; 2009. Available from: **www.cebm.net/index.aspx?o=1025**. Accessed 2010 Nov 30.
38. Sharma M, Arnason JT, Burt A, Hudson JB. Echinacea extracts modulate the pattern of chemokine and cytokine secretion in rhinovirus-infected and uninfected epithelial cells. *Phytother Res* 2006;20(2):147-52.
39. Barrett B. Medicinal properties of Echinacea: a critical review. *Phytomedicine* 2003;10(1):66-86.
40. Raduner S, Majewska A, Chen J, Xie X, Hamon J, Faller B, et al. Alkylamides from echinacea are a new class of cannabinomimetics. Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. *J Biol Chem* 2006;281(20):14192-206. Epub 2006 Mar 17.
41. Linde K, Barrett B, Wölkart K, Bauer R, Melchart D. Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2006;(1):CD000530.
42. Dorn M, Knick E, Lewith G. Placebo-controlled, double-blind study of Echinaceae pallidae radix in upper respiratory tract infections. *Complement Ther Med* 1997;5(1):40-2.
43. Lindenmuth GF, Lindenmuth EB. The efficacy of echinacea compound herbal tea preparation on the severity and duration of upper respiratory and flu symptoms: a randomized, double-blind placebo-controlled study. *J Altern Complement Med* 2000;6(4):327-34.
44. 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* 2002;137(12):939-46.
45. Mullins RJ, Heddle R. Adverse reactions associated with echinacea: the Australian experience. *Ann Allergy Asthma Immunol* 2002;88(1):42-51.
46. Huntley AL, Thompson Coon J, Ernst E. The safety of herbal medicinal products derived from Echinacea species: a systematic review. *Drug Saf* 2005;28(5):387-400.
47. 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* 2003;290(21):2824-30.
48. Block KI, Mead MN. Immune system effects of echinacea, ginseng, and astragalus: a review. *Integr Cancer Ther* 2003;2(3):247-67.
49. Pannacci M, Lucini V, Colleoni F, Martucci C, Grosso S, Sacerdote P, et al. Panax ginseng C.A. Mayer G115 modulates pro-inflammatory cytokine production in mice throughout the increase of macrophage toll-like receptor 4 expression during physical stress. *Brain Behav Immun* 2006;20(6):546-51.
50. Scaglione F, Ferrara F, Dugnani S, Falchi M, Santoro G, Fraschini F. Immunomodulatory effects of two extracts of Panax ginseng C.A. Meyer. *Drugs Exp Clin Res* 1990;16(10):537-42.
51. 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* 2009 Jul 10. Epub ahead of print.
52. Seely D, Dugoua JJ, Perri D, Mills E, Koren G. Safety and efficacy of Panax ginseng during pregnancy and lactation. *Can J Clin Pharmacol* 2008;15(1):e87-94. Epub 2008 Jan 18.
53. Coon JT, Ernst E. Panax ginseng: a systematic review of adverse effects and drug interactions. *Drug Saf* 2002;25(5):323-44.
54. Pauling L. The significance of the evidence about ascorbic acid and the common cold. *Proc Natl Acad Sci U S A* 1971;68(11):2678-81.
55. Wintergerst ES, Maggini S, Hornig DH. Immune-enhancing role of vitamin C and zinc and effect on clinical conditions. *Ann Nutr Metab* 2006;50(2):85-94. Epub 2005 Dec 21.
56. Reinhart KM, Talati R, White CM, Coleman CI. The impact of garlic on lipid parameters: a systematic review and meta-analysis. *Nutr Res Rev* 2009;22(1):39-48.
57. Ried K, Frank OR, Stocks NP, Fakler P, Sullivan T. Effect of garlic on blood pressure: a systematic review and meta-analysis. *BMC Cardiovasc Disord* 2008;8:13.
58. Ngo SN, Williams DB, Cobiac L, Head RJ. Does garlic reduce risk of colorectal cancer? A systematic review. *J Nutr* 2007;137(10):2264-9.
59. Higdon J, Drake VJ, Lawson LD. *Garlic and organosulfur compounds.* Corvallis, OR: Linus Pauling Institute, Oregon State University; 2008. Available from: **http://lpi.oregonstate.edu/infocenter/phytochemicals/garlic**. Accessed 2009 Oct 25.
60. Ankri S, Mirelman D. Antimicrobial properties of allicin from garlic. *Microbes Infect* 1999;1(2):125-9.
61. Lenoir-Wijnkoop I, Sanders ME, Cabana MD, Caglar E, Corthier G, Rayes N, et al. Probiotic and prebiotic influence beyond the intestinal tract. *Nutr Rev* 2007;65(11):469-89.
62. De Vrese M, Schrezenmeir J. Probiotics and non-intestinal infectious conditions. *Br J Nutr* 2002;88(Suppl 1):S59-66.
63. Yasui H, Shida K, Matsuzaki T, Yokokura T. Immunomodulatory function of lactic acid bacteria. *Antonie Van Leeuwenhoek* 1999;76(1-4):383-9.
64. Vouloumanou EK, Makris GC, Karageorgopoulos DE, Falagas ME. Probiotics for the prevention of respiratory tract infections: a systematic review. *Int J Antimicrob Agents* 2009;34(3):197.e1-10. Epub 2009 Jan 28.
65. Novick SG, Godfrey JC, Godfrey NJ, Wilder HR. How does zinc modify the common cold? Clinical observations and implications regarding mechanisms of action. *Med Hypotheses* 1996;46(3):295-302.
66. Eby GA, Halcomb WW. Ineffectiveness of zinc gluconate nasal spray and zinc orotate lozenges in common-cold treatment: a double-blind, placebo-controlled clinical trial. *Altern Ther Health Med* 2006;12(1):34-8.
67. Belongia EA, Berg R, Liu K. A randomized trial of zinc nasal spray for the treatment of upper respiratory illness in adults. *Am J Med* 2001;111(2):103-8.
68. Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat J* 2000;79(10):778-80, 782.
69. Mossad SB. Effect of zincum gluconicum nasal gel on the duration and symptom severity of the common cold in otherwise healthy adults. *QJM* 2003;96(1):35-43.
70. Godfrey JC. Zinc for the common cold. *Antimicrob Agents Chemother* 1988;32(4):605-6.
71. Jackson JL, Lesho E, Peterson C. Zinc and the common cold: a meta-analysis revisited. *J Nutr* 2000;130(5S Suppl):1512S-5S.
72. Zarembo JE, Godfrey JC, Godfrey NJ. Zinc(II) in saliva: determination of concentrations produced by different formulations of zinc gluconate lozenges containing common excipients. *J Pharm Sci* 1992;81(2):128-30.
73. Cohen DA. The efficacy of zinc lozenges and zinc nasal sprays in the treatment of the common cold. *Top Clin Nutr* 2006;21(4):355-61.
74. Marshall S. Zinc gluconate and the common cold. Review of randomized controlled trials. *Can Fam Physician* 1998;44:1037-42.

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