ECHINACEA AND GINSENG FOR IMMUNOMODULATION AND PREVENTION OF RESPIRATORY INFECTION

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Summary

Several decades of research on extracts of *Echinacea* spp. in various laboratory models have confirmed immunomodulatory activity. Some sixteen clinical trials involving an echinacea-containing formulation have tested efficacy as treatment for upper respiratory infection (common cold). Another eight have tested ability to prevent infectious illness. While the majority of trials have reported positive results, four of the most recent and highest quality trials have not found benefit. Strength of evidence for ability of echinacea extracts to prevent illness is judged to be similar to strength of evidence regarding ability to reduce symptom severity. While research on *Ginseng* spp. extracts for immunomodulation and respiratory infection is more sparse, an emerging literature points to both immune activity and potential preventive efficacy. Four clinical trials testing two very different ginseng extracts have all been reported positively. No published trials have tested products containing both echinacea and ginseng components.

Key words: common cold, echinacea, ginseng, immune system, immunomodulation, infectious disease, respiratory infection

Various extracts from the botanical genera *Echinacea* and *Ginseng* are in wide use, with immune enhancement and prevention or treatment of acute respiratory infection as stated rationale. The broad purpose of this paper is to provide a literature review and summary of current scientific evidence regarding ability of echinacea and ginseng extracts to affect the immune system, and to prevent or treat acute upper respiratory infection (aka. common cold.).

Methods

Using electronic databases such as PubMed/MedLine and library assistance, I conducted a systematic review of available evidence regarding immunomodulation and prevention of acute respiratory infection (ARI) for preparations derived from echinacea (*Echinacea purpurea, E. angustifolia*, or *E. pallida*), or ginseng (*Panax ginseng* or *P. quinquefolium*). Multiple literature searches using various search terms were completed for echinacea and for ginseng during 2005 and 2006. Published articles were read in detail. Bibliographies were reviewed and references retrieved and studied. Discussions with experts provided additional information.

Results - Echinacea

Extracts of *Echinacea purpurea, E. angustifolia, E. pallida* are widely used for prevention and treatment of acute respiratory infection. "Immune enhancement," "immune stimulation" or "immune boosting" are the purported rationale for preventive therapy. A reasonably broad body of scientific literature does in fact suggest that various echinacea extracts do exhibit some immunomodulating properties (1-12). Enhanced macrophage (13-18) and NK cell activity (19-25) are perhaps the best established. Increased granulocyte activity has also been reported (26;27). These findings come from *in vitro*, *in vivo* and *ex vivo* experiments, using various chemical assays, cultured cells, and in a few cases, live animals. Relevance to human health is possible, but not certain, as 1) immunomodulation has not been unequivocably shown in clinical (human) studies, and 2) enhanced immune activity may or may not translate into increased resistance to disease or to better health.

Echinacea's effects on antibody production is controversial, as evidence is limited. Bodinet and Freudenstein reported enhanced production of antibody to sheep red blood cell antigen in mice (28). Bodinet et al. also reported enhanced immune response and better survival among mice infected with influenza A (29). Freier reported increases in IgM antibody-forming cell response in mice given oral echinacea extract compared to controls (30). Rehman reported enhanced IgG response to KLH antigen in rats (31). To date, there are no published reports of echinacea's effects on human antibody production, or investigations of echinacea as a human vaccine adjuvant.

The bulk of echinacea clinical research concerns ARI (common cold aka. upper respiratory infection, presumed viral). There are at least 16 clinical trials testing an echinacea-containing preparation as treatment for common cold, and eight trials evaluating echinacea extracts for prevention. The majority of treatment trials, including several with reasonably good methodological quality, have reported positive results (32-41).

For instance, Bräunig, Brinkenorn, Hoheisel, and Schulten all reported benefits of various *E. purpurea* formulations in trials that were described as randomized and double-blind (32;35;36;40). Dorn and Vorberg each reported a positive trial of formulation derived from *E. angustifolia* (33;42). Bräunig (37) positively reported a trial testing an extract of *E. pallida*; however, this same trial was later reported more negatively by Dorn (43). Voberg, Reitz, and Henneicke-von Zepelin each reported trials using a product that combined extracts of *E. purpurea* and *E. pallida* (41;44;45). While a few of these positively-reported trials have described reductions in the duration of illness (35;38;40), most reported benefits in terms of symptom reduction, using various self-report measures. Improvement in nasal symptoms and/or global symptom severity have been the main outcomes, and have been in the 10% to 40% effect size range (32-41). Nearly all of trials were manufacturer-sponsored. Methodological quality is judged as moderate for most of these trials, with lack of proof of blinding the most common limitation.(46-48).

Four recent treatment trials have found no benefit (49-52). These include two from Wisconsin USA in which adults with community acquired colds were randomized to echinacea or placebo at the onset of symptoms (49;52). My trial among 148 college students in Madison WI was the first negatively-reported echinacea treatment trial (49). The Yale trial from Marshfield WI among 128 adults also failed to find benefit (52). The Taylor trial from Seattle, Washington, randomized 407 children to echinacea or placebo over a total of 707 cold episodes (50), and found neither symptomatic nor duration benefit. The most recent negative trial by Turner involved 399 college-aged volunteers who were randomized to one of three echinacea preparations, either as prevention or treatment, before or after inoculation with rhinovirus. There were seven groups in total, so power was limited due to sample size (51). Of these, only the Taylor trial was large enough to have the power to detect between-group differences of 20% or less.

Unfortunately, there are few common unifying factors to explain why the earlier treatment trials appeared positive, while the later three trials were negative. Interestingly, the four negative trials are all from the U.S., while the positive trials all come from Europe or Canada. Also, all positive trials were industry-sponsored, versus public-sponsorship of most of the negative research. Phytochemical content and dose regimen do not easily explain these discrepancies either. However, most of the positive trials have tested preparations made from above-ground portions of *E. purpurea*, leading the 2006 Cochrane systematic reviewers (53) to conclude "There is some evidence that preparations based on the aerial parts of *Echinacea purpurea* might be effective for the early treatment of colds in adults but results are not fully consistent. Beneficial effects of other Echinacea preparations, and for preventive purposes might exist but have not been shown in independently replicated, rigorous randomized trials."

Although I was one of these authors, I am not convinced that the evidence is sufficient to single out *E. purpurea* preparations as more likely to benefit. Instead, I feel that the age and immune status of the subjects may be more important. Participants were young and healthy in all the negative trials, and older and possibly more immune-limited in many of the positive trials. Potential biases related to the sponsorship of trials may be an even more important factor.

While conventional wisdom (within the pro-echinacea camp) has tended to support treatment rather than preventive efficacy, it seems to me that the prevention hypothesis enjoys substantial support. Of the eight randomized controlled trials (RCTs) testing echinacea for prevention of respiratory infection, three were reported positively (54-56), with the other five all trending in a positive direction (51;57-60). Three of these used an induced-cold rhinovirus model. In Sperber's trial, 14 of 24 (58%) treated with echinacea developed symptomatic colds, compared with 21 of 22 (88%) in the placebo-treated group (59). In Turner's first trial, 11 of 50 (22%) treated with echinacea developed colds, versus 14 of 42 (33%) in the placebo group.(60) In Turner's second trial, 73 of 149 (49%) treated with echinacea developed colds, compared with 58 of 103 (56%) in the placebo group (51). Schoop et al. pooled data from these trials in a 2006 meta-analysis, reporting that "the likelihood of experiencing a clinical cold was 55% higher with placebo than with echinacea (O.R. 1.55 [95% CI, 1.02 - 2.36]; $p < 0.043$"(61).

Of the five community-acquired cold prevention trials, three included non-echinacea constituents (54-56). The three earliest trials reported incidence reductions of 49% ($p<0.05$) (55), 15% ($p=0.08$) (56), and 14% ($p=0.10$) (this last trial was reported twice (58;62)). A more recent preventive trial among 430 children was reported as positive, with 138 colds in the treatment group vs. 308 in the placebo group ($P<0.001$) (54). The two trials reporting the greatest benefits (54;55) were also the most limited methodologically. Perhaps the highest quality prevention trial is Melchart's RCT (N=302) reported in 1998 (57). This 3-armed RCT tested extracts of *E. purpurea* root and *E. angustifolia* root against placebo, reporting relative risks of 0.80 and 0.87 respectively, compared to placebo. Although these positive trends were not statistically significant, they were consistent and in the expected direction (57). The authors concluded "In this study a prophylactic effect of the investigated echinacea extracts could not be shown. However, based on the results of this and two other studies, one could speculate that there might be an effect of echinacea products in the order of magnitude of 10% to 20% relative risk reduction." Finally, it should be noted that the largest and arguably highest quality treatment trial (Taylor) found that 52% of those randomized to echinacea went on to second colds, compared with 64% treated with placebo ($p=0.015$) (50). A separately published analysis of these data concluded that "use of echinacea was associated with a 28% decreased risk of subsequent URI ($p = 0.01$; 95% CI = 8%-44% decreased risk)"(63).

Collectively, these findings can be interpreted as suggestive evidence of some ARI preventive effect, with estimates of effect size centering from 10% to 28% reduction in incidence. Interpretation of treatment trials is more problematic, as several examples of high-quality negative trials co-exist with about a dozen positive trials of lower methodological quality.

Results – Ginseng

Ginseng commands a larger global market than echinacea, primarily due to demand from Asia. The use of ginseng, however, is guided by principles much different than that of echinacea. While echinacea is used to boost the immune system and prevent or treat infectious respiratory disease, the use of ginseng is aimed more at achieving or maintaining a healthy balance. Westerners as well as Chinese attribute "adaptogenic" properties (64-66) to ginseng, and often invoke or describe "balance," "equilibrium," or "homeostatis" when translating principles and practice of traditional Chinese medicine (67). The concept of "immunomodulation" (68-70) may be more in accordance with Chinese traditional Chinese thought than "immunosimulation," as "modulation" implies balancing of multiple domains, wheras "stimulation" assumes a linear immune system that can only be increased or decreased.

Both pre-clinical and clinical research for ginseng is less focused than that for echinacea. There is a broad literature suggesting that various ginseng (*Panax* spp) extracts may effect various metabolic parameters (71-80). However, many published results have not been replicated, and clinically useful evidence from randomized trials is limited if not absent (81-83). Nevertheless, a growing body of research suggests that ginseng extracts may influence various immune mechanisms, including both specific (adaptive) and nonspecific (innate) pathways (68;84-96). Enhancement of natural killer cell activity has been reported by several different research groups (24;96-99). A few live animal studies suggest adaptive immune enhancement in the form of vaccine adjuvant activity (99-104). Some reports appear to endorse the balanced-immunomodulatory conceptual framework. For example, Rivera et al. reported that "ginseng elicits a balanced Th1 and Th2 immune response," describing effects on IFN-gamma, IL-2, IL-4, IL-10 and TNF-alpha, and an increase in antibody levels (105).

Two distinct ginseng preparations have been reported positively in clinical trials assessing ability to prevent respiratory infection. One widely used extract of *Panax ginseng* - standardized to 4% ginsenosides (triterpene saponins) - was tested in a double-blinded RCT in Italy and reported by Scaglione et al. in 1996 (106). Participants (N= 227) in this trial were followed for 12 weeks of once daily dosing of 100mg of this extract of Korean (aka. Aisan) ginseng. Outcomes measured included: 1) number of ARI illness episodes, and 2) antibody response to influenza vaccination,

which was done in the fourth week of the trial. The authors reported fewer colds in the ginseng group compared to placebo group (42 vs.15 cases; $p<0.001$). Antibody levels and natural killer (NK) activity were assessed at weeks 4, 8 and 12. Participants in the ginseng group demonstrated both higher antibody titer (272 vs. 171 units; $p <0.001$) and NK activity (46.0 vs. 26.7; $p<0.001$) during week 8. Apparent effects were less prominent during the other weeks. Although highly intriguing, this trial was limited by lack of proof of blinding, by lack of important detail regarding laboratory procedures and statistical techniques, and by the fact that this was a manufacturer-sponsored trial without any public interest oversight.

An entirely different ginseng extract has been tested for immunomodulatory activity and for ability to prevent ARI in a series of investigations from Canada. The product is an extract of *Panax quinquefolium* (American ginseng) that contains substantial amounts of various oligosaccharides and polysaccharides, but very little in the way of ginsenoside saponins. Pre-clinical studies of this product describe stimulation and proliferation of cultured mouse spleen cells exposed to the extract, with enhanced production of IFN-γ, IL-2, IL-6, TNF-α, and nitrous oxide reported (107;108). Dose-dependency and between-batch consistency was reported in the second of these studies (108).

Three randomized controlled trials have been carried out on this American ginseng derived oligo- and poly-saccharide-rich formulation. The first involved 43 elderly adults who took 400mg of this product daily for four months (109). A secondary analysis of the data suggested possible ARI prevention effects, especially during the last two months of observation. Other outcomes and rates of possible side effects were similar in active and placebo groups. This trial was carried out in 1998 but the report was not published until 2006.

The second trial was a double-blinded RCT done in the 2000 and 2001 influenza seasons and reported McElhaney et al. in 2004 (110). In the first year of this study, 89 elderly nursing home residents took 200mg of this polysaccharide-rich extract (or placebo) once daily for 8 weeks; in the second phase, 109 particpants took the same pills but were monitored for 12 weeks. All in all, there were101 evaluable subjects in the placebo group, and 99 in the ginseng group. Participants were interviewed twice weekly for signs of ARI. Combining both years there were a total of 36 ARI episodes in the placebo group and 33 in the ginseng group (small positive trend not significant). Influenza culture, however, revealed 7 confirmed cases of influenza in the placebo group versus 1 case in the ginseng group) (Mantel-Haenszel odds ratio 7.7, $P=0.03$). Monitoring for adverse effects revealed no significant differences or meaningful trends. Although randomization appeared adequate, evidence of blinding was not presented.

The third trial evaluating the Canadian ginseng extract was reported by Predy et al. in 2005 (111). This double blind trial randomized 323 subjects aged 18 to 65 to either 400mg daily of the same polysaccharide-rich *Panax quinquefolium* extract (N=153), or to matched placebo (N=170). A total of 149 in the placebo group and 130 in the ginseng group were monitored for four months. Using standardized ARI symptom criteria, these authors reported that 95 people (64%) in the placebo group and 71 people (55%) in the ginseng group had at least one ARI illness (common cold) episode. This was statistically significant at $p<0.01$, corresponding to a 9% absolute reduction in risk of illness, or a number needed to treat of about 11. Similarly, 34 (23%) in the placebo group had ≥ 2 colds, compared with 13 (10%) in the ginseng group. Of those who had at least one cold, the average duration was 16.5 days and the total symptom score 112 in the placebo group versus 10.8 days and 77 in the ginseng group. All of these apparent benefits were statistically significant at $p < 0.05$, most at <0.01. There was no suggestive evidence of adverse effects attributable to the ginseng formulation. Evidence of both randomization and blinding were presented and were credible. Limitations include lack of data on those lost to follow-up, and lack of generalizability to elderly populations. People over 65 and those who had received a flu shot in the previous 6 months were excluded, hence those that most need protection from ARI were not represented.

Discussion

In terms of numbers of trials and numbers of participants, there is more evidence regarding the ability of echinacea to prevent or treat the common cold than for any specific conventional medicine. While it is reasonably clear that decongestants, especially nasal formulations, can reduce congestion and drainage, this conclusion is based on only a few trials (112). Evidence on antihistamines is less convincing, but there are a few good quality trials suggesting that the anticholinergic effects of first-generation (sedating) antihistamines may also reduce nasal mucus production (113). No multiple component formulations have been shown effective in high quality independent trials. Nasal saline and nasal steroids may reduce symptoms, but have very little support from RCTs (114-117). Evidence for the effectiveness of Vitamin C and zinc is similar to that for echinacea, in that multiple RCTs have provided a fair amount of both positive and negative evidence (118;119). While good nutrition, regular exercise, and hand-washing are certainly important, no specific interventions have been shown to be prevent upper respiratory infections. Immunomodulation has not yet been clearly shown to be of benefit for prevention or treatment of respiratory infection.

Unlike echinacea, where several public-interest trials have been complete, all of the ginseng trials to data have been manufacturer-sponsored. Given the fact that all public-interest echinacea ARI trials have been negative and nearly all manufacturer-

sponsored trials positive, I suggest caution in interpreting the three existing ginseng trials. Notwithstanding these concerns, it can be noted that all three published trials are of moderate to good quality, and all report statistically significant benefits (Scaglione, Predy) or trends toward benefit (McElhaney), hence larger, publicly funded trials are clearly warranted. Whether these positive trials will be substantiated, refuted, or eclipsed by future research cannot be predicted at this time.

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