Complementary medicine for treating or preventing influenza or influenza-like illness

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CRD summary
The review concluded there was limited evidence of the effectiveness of complementary and alternative therapies for treatment or prevention of influenza or influenza-like illness, which strengthens evidence for the use of conventional treatments for seasonal influenza. The reliability of the authors’ cautious conclusions is uncertain due to lack of reporting of validity assessment and lack of trial details.

Authors’ objectives
To evaluate the effectiveness of complementary and alternative therapies for the prevention or treatment of influenza or influenza-like illness such as avian influenza.

Searching
MEDLINE, EMBASE, the Cochrane Library, CINAHL and AMED were searched from inception to June 2006 with no language restrictions. Search terms were reported. Reference lists of identified articles were scanned for additional studies. Manufacturers of commercial products and experts in the field were contacted for additional studies.

Study selection
Randomised controlled trials (RCTs) evaluating any complementary and alternative therapy, in comparison with placebo or control, against active antiviral medication in participants of either sex or any age were eligible for inclusion. To be included participants had to be clinically diagnosed with influenza or influenza-like illness and prevention trial participants had to be healthy. Trials that evaluated the immune responses to influenza vaccination as the only outcome measures were excluded. Trials assessing all clinically relevant outcomes including adverse events were eligible for inclusion.

The included trials assessed: Sambucus nigra (elderberry, commercial brand Sambucol); Panax quinquefolium (North America Ginseng, CVT-E002 extract); Echinacea purpurea (Echinacea root extract); Kan Jang (herbal extracts); Gan Mao Jiao Nan (GMJN, single and combination Chinese herbal preparations); Oscillococcinum (homeopathic preparation); and Mucococcinum (homeopathic preparation). Seven trials were placebo controlled. Tables providing additional characteristics of included trials were not available in the review.

Two reviewers independently selected studies and resolved disagreements through discussion and, if necessary, through consultation with a third author.

Assessment of study quality
Validity assessment was conducted using the Jadad score (the maximum score of 5 for the highest quality). In addition selection, performance, attrition and detection were assessed (scored using ‘yes’, ‘no’ or ‘don’t know’).

Two reviewers independently assessed validity and resolved disagreements through discussion and, if necessary, through consultation with a third author.

Data extraction
Where necessary effect sizes and their 95% confidence intervals (CIs) were calculated. Results from continuous data were calculated as mean difference (MD). Results from dichotomous data were calculated as risk ratio (RR). Due to the low number of events in two studies, the Peto odds ratio (Peto OR) was used instead of RR.

Data were extracted by one reviewer and checked by a second reviewer using a standard form.

Methods of synthesis
Trials were grouped into treatment and prevention categories. In addition, each group was split into sub groups of placebo-controlled trials and active controlled trials. Where appropriate data were pooled. The pooled weighted mean difference was calculated where appropriate. Heterogeneity was assessed using $\chi^2$ test.

**Results of the review**

Fourteen RCTs (n=unknown) were included. Three RCTs scored a maximum of 5 points on the Jadad scale, three RCTs scored 4 points, two RCTs scored three points, five RCTs scored two points and one RCT scored one point.

**Treatment (10 RCTs):**
A greater improvement in symptoms (one RCT, n=40), and a reduction of the duration of symptoms by four days (one RCT, n=60), was reported for participants treated with Sambucus nigra compared to placebo. A high dose of Echinacea purpurea extract (900mg) was found to be more beneficial than placebo for symptom reduction at 3, 4, 8 and 10 days (one RCT, n=120). However, no significant differences were found comparing a lower dose of Echinacea purpurea extract (450mg) and placebo. Responder rates for complete symptom resolution within 48 hours (two RCTs, n=850) were greater for Oscillococcinum use compared to placebo and there was also a beneficial effect on duration of symptoms (two RCTs, n=850); no evidence of statistical heterogeneity was found for this analysis.

There was a significantly lower risk of participants using Kan Jang developing secondary infection-induced complications compared to an active comparator and a reduction in sick leave (one RCT, n=66). Responder rates for symptom resolution within 48 hours was significantly higher for participants treated with Gan Mao Jiao Nan in comparison with Amantadine (one RCT, n=213).

**Prevention (four RCTs):**
Fewer cases were reported of influenza for participants receiving Panax quinquefolium compared with placebo (two RCTs, n=198), or Gan Mao Jiao Nan compared to Amantadine (one RCT, n=738). No statistically significant differences were found between Oscillococcinum or placebo groups for the incidence of influenza-like illness (one RCT, n=1,573) or between Mucococcinum and placebo groups for number of reported symptoms (one RCT).

**Adverse Events:**
There were a high number of incidents of adverse events reported for Panax quinquefolium. Fifty percent of these adverse events were gastrointestinal symptoms and were mainly mild to moderate in severity and some serious adverse events were not related to trial medication (one RCT). There was a significantly higher incidence of adverse events in the Oscillococcinum group compared to placebo (one RCT). No adverse events were observed in three trials and the remaining trials did not monitor adverse events.

**Authors’ conclusions**

There was limited evidence of the effectiveness of complementary and alternative therapies for treatment or prevention of influenza or influenza-like illness. The results from this review therefore strengthen evidence for the use of conventional treatments for seasonal influenza. There was no data available on avian influenza.

**CRD commentary**

The review question was clear in terms of study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to minimise publication and language bias. Two reviewers independently selected studies, assessed validity and extracted data, thus reducing the potential for reviewer bias and errors. Validity was assessed using specified criteria but only the results of assessment using the Jadad scale were reported in the review. Additional tables containing trial characteristics were not available online or from the review authors, which is of particular importance as not all the results were reported for the validity assessment and it is not possible to evaluate other potential biases of the included trials. A narrative synthesis was appropriate given the differences in the complementary and alternative therapies. However, as characteristics of trials were unavailable, it is not possible to determine whether pooling of some studies was appropriate. Although tests of statistical heterogeneity were conducted, these were only reported for some analyses. The reliability of the authors' cautious conclusions is uncertain due to lack of reporting of some aspects of the validity assessment and lack of details of individual trials.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that large, methodologically robust, independent studies are needed to evaluate the effectiveness of complementary and alternative therapies. Specific strains of the influenza virus need to be evaluated in separate studies. Future studies should include large sample sizes and should include older, more vulnerable participants.

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