Efficacy of dry extract of ivy leaves in children with bronchial asthma: a review of randomized controlled trials

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CRD summary
This review investigated if extracts from dried ivy leaves (Hedera helix L.) are effective in the treatment of chronic airway obstruction in children suffering from bronchial asthma. Limited evidence suggested that ivy leaf preparations may lead to improvement of respiratory functions. While the results of the review appeared promising, they were based on limited and low quality evidence.

Authors' objectives
To investigate whether extracts from dried ivy leaves (Hedera helix) were effective in the treatment of chronic airway obstruction in children with bronchial asthma.

Searching
Eligible trials were identified by searching MEDLINE (from 1966 to 2001) and EMBASE (from 1974 to 2001), as well as German medical journals not indexed in the databases and lay publications. The search terms were presented in the report. The bibliographies of obtained articles were also checked. There were no language restrictions.

Study selection
Study designs of evaluations included in the review
The studies needed to be randomised with a placebo or reference control group. Two of the included trials were crossover double-blind, while the other was crossover open. Two were designed as non-inferiority (or equivalence) trials.

Specific interventions included in the review
The interventions had to involve treatment with ivy leaf extract (any form of administration). The included trials compared ivy leaf extract cough drops with placebo, suppositories with drops and syrup with drops. Ivy leaf extract was manufactured under the name of Prospan, the manufacturers of which sponsored the research. The doses were 35 to 42 mg/day for drops, 160 mg/day for suppositories and 105 mg/day for syrups. The larger doses of the suppository and syrup formulations were explained as being due to the special characteristics of ethanol-free formulations.

Participants included in the review
The participants needed to be children with airway obstruction for whom appropriate informed consent had been obtained. The trials included children aged from 4 to 16 years.

Outcomes assessed in the review
It was unclear whether the outcomes were pre-specified. Airway resistance was the primary outcome in all three included trials.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
No formal assessment of validity was reported, but the authors considered allocation of concealment and the primary characteristics of the selected trials and their results. Judgements of methodological quality were made by the authors independently.
Data extraction
Changes from applicable baselines and differences between treatment conditions, along with 95% confidence intervals, were determined. The calculations were based on intention-to-treat analysis in the case of placebo control, and on per protocol analysis in the case of reference-controlled trials designed to establish equivalence/non-inferiority. Non-parametric tests were used in the analysis due to the non-normality of the data and for comparison with the original publications.

Methods of synthesis
How were the studies combined?
The studies were combined narratively and the results were tabulated for comparative purposes. In addition, indirect comparisons were carried out, using a published method, to ascertain whether suppositories or syrup were superior to placebo.

How were differences between studies investigated?
Differences between the included trials were highlighted within the report.

Results of the review
Three trials with a total of 75 participants were included.

Efficacy.
Drops containing ivy leaf extract were significantly superior to placebo in reducing airway resistance (P=0.04). Syrup and suppositories showed non-inferiority in comparison with drops.

Safety.
Four patients in one of the included trials suffered an intercurrent respiratory tract infection, which was described as unrelated to the treatment. In one trial, one patient showed an exacerbation of an existing atopic dermatitis with possible relationship to ivy leaf suppositories. The other trial observed no adverse events.

Authors' conclusions
The ivy leaf extract preparations improved respiratory functions in children with chronic bronchial asthma, but more detailed conclusions could not be drawn due to the limited data and the fact that only one trial included a placebo control.

CRD commentary
This review had defined inclusion criteria for the participants, intervention, outcomes and study design. Two databases were searched and a range of other methods were used to locate research. It is possible that research was missed since the authors did not consult a database specific to complementary medicine. The validity assessment was limited, and little detail on the quality of the three included trials was provided. It was unclear whether more than one reviewer was involved in each stage of the review process, which could help to minimise bias. While the results of the review appeared promising, it should be noted that they were based on the results of one small placebo-controlled trial and indirect comparisons of the extract in suppository and syrup form. The review's authors indicated that the research points to the need for larger trials. Such trials, if appropriately powered, would also allow a closer examination of the safety profile of ivy leaf extract.

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

Research: The authors stated that, as the trials in this review only considered short-term effects, further research is
needed into the long-term efficacy of ivy leaf extract. They also highlighted the need for additional placebo-controlled trials with appropriate methodology and larger patient numbers.

**Funding**
Engelhard Arzneimittel GmbH and Co.

**Bibliographic details**

**PubMedID**
12725580

**DOI**
10.1078/094471103321659979

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Asthma /drug therapy; Child; Hedera; Humans; Phytotherapy; Plant Extracts /therapeutic use; Randomized Controlled Trials as Topic; Treatment Outcome

**AccessionNumber**
12003009675

**Date bibliographic record published**
31/03/2004

**Date abstract record published**
31/03/2004

**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.