Interactions between herbal medicines and prescribed drugs: a systematic review

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Authors' objectives
To determine the possible interactions between the seven top-selling herbal medicines (ginkgo, St. John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and prescribed drugs.

Searching
MEDLINE (via PubMed), EMBASE, the Cochrane Library (Issue 2, 2000) and PHYTObase were searched from their inception to July 2000. The search terms were the seven selected medicinal plants (English and German common names as well as botanical denominations) in combination with the following terms: 'drug interaction', 'adverse-effects', 'side-effects', 'adverse drug reaction', 'safety' and 'toxicity'. In addition, recent books and articles on herb-drug interactions or herbalism, recent reviews of the seven selected medicinal plants, all reference lists, and the authors' files were searched. Major manufacturers of herbal products, experts and organisations related to herbalism were contacted for additional material. Reports in any language were considered.

Study selection
Study designs of evaluations included in the review
Case reports, case series, clinical trials and other types of investigation were eligible. In vitro experiments were usually excluded. Studies of the following designs were included: randomised controlled trials (RCTs), both single- and double-blind; non-randomised controlled trials; before-and-after studies; case series; and case reports.

Specific interventions included in the review
Combinations of any of seven herbal medicines (ginkgo, St. John's wort, ginseng, garlic, echinacea, saw palmetto and kava) and conventional prescribed drugs were eligible.

Participants included in the review
People taking conventional prescribed drugs were eligible.

Outcomes assessed in the review
Articles that reported herb-drug interactions were eligible.

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

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The first author extracted the following data into predefined tables, while the second author validated the extracted data: herbal medicine, dosage, and duration; gender, number and diagnosis of participants; prescribed drug, dosage and duration; concomitant drugs; clinical result of interaction; and possible mechanism.

Methods of synthesis
How were the studies combined?
The studies were grouped according to medicinal plant and a narrative synthesis was undertaken.
How were differences between studies investigated?
The authors do not report any investigation of differences between the studies.

Results of the review
Seventeen clinical trials (91 patients) and 41 case reports (79 patients) were included.

Methodological flaws in the primary studies included a failure to adequately define the botanical agents used; and case reports that did not clearly distinguish between adverse events due to toxicity and those due to herb-drug interactions.

Garlic (1 before-and-after study and 3 case reports). Concomitant use of garlic and paracetamol may be associated with changes in pharmacokinetic variables of paracetamol after 1 to 3 months' treatment (1 before-and-after study with 16 patients). Concomitant use of garlic and warfarin was associated with an increase in the international normalised ratio (INR) in 2 case reports. One case of hypoglycaemia was reported in a diabetic taking garlic and chlorpropamide.

Ginkgo (1 RCT, 1 before-and-after study and 4 case reports).

Ginkgo interactions include spontaneous bleeding when combined with warfarin (2 case reports), raised blood-pressure when combined with a thiazide diuretic (1 case report), and coma when combined with trazodone (1 case report). Ginkgo did not modify the half-life of antipyrine (1 RCT before-and-after study with 25 patients), and did not modify hormonal plasma levels after stimulation tests with luteinising hormone-releasing hormone or thyrotropin-releasing hormone (1 before-and-after study with 7 patients).

St. John's wort (2 RCTs, 2 non-randomised controlled trials, 6 before-and-after comparisons, 4 case series and 26 case reports).

St. John's wort was reported to lower the blood concentration of cyclosporin (3 case series with 45 patients and 5 case reports), amitriptyline (1 non-blind study with 12 patients), digoxin (1 placebo controlled trial with 25 patients), indinavir (1 before-and-after study with 8 patients), warfarin (1 placebo-controlled crossover RCT with 10 healthy patients, and 7 case reports), phenprocoumon (1 case report), and theophylline (1 case report). It also caused intermenstrual bleeding when used concomitantly with oral contraceptives (1 case series with 8 patients and 4 case reports), and delirium or mild serotonin syndrome when used concomitantly with loperamide (1 case report) or selective serotonin re-uptake inhibitors (7 case reports).

St. John's wort in combination with alcohol was found to result in no change in cognitive function (1 placebo-controlled, double-blind crossover RCT with 32 patients), or in vigilance with either alcohol alone or in combination with valarian (1 non-blind study with 12 patients). Four out of five before-and-after studies found an increase or a trend to increase the metabolic capacity of cytochrome P450 enzymes.

Ginseng (1 placebo-controlled RCT with 227 patients, 1 before-and-after with 14 patients, and 3 case reports).

Ginseng was reported to lower the blood concentration of alcohol (before-and-after with 14 patients), and not change any safety parameters when used in combination with influenza vaccine (1 RCT with 227 patients). However, it was found to induce mania (1 case report) or insomnia and headaches (1 case report) when used with phenelzine.

Kava (1 placebo-controlled RCT and 2 case reports).

Kava was reported to not change safety parameters when taken with alcohol (1 RCT with 20 patients). However, it increased 'off' periods in Parkinson patients taking levadopa (1 case report), and caused a semi-comatosed state when used with alprazolam, cimetidine and terazosin (1 case report). No interactions were found for echinacea and saw palmetto.

Authors' conclusions
Interactions between herbal medicines and synthetic drugs exist and can have serious clinical consequences.
CRD commentary
The aims were stated and the inclusion criteria were broadly defined in terms of the study design, interventions, participants and outcome. Several relevant sources were searched, attempts were made to locate unpublished material, and no language restrictions were applied. No details were given of the methods used to select the studies, and the validity of the included studies was not assessed. Some relevant data were tabulated and the methods used to extract the data were described. A narrative review was appropriate given the small number of studies of similar design for individual herbal drugs. No account was taken of the quality of the studies when combining them, although the authors did advise caution when interpreting evidence from case reports.

The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that health care professionals should ask their patients about the use of herbal products and consider the possibility of herb-drug interactions.

Research: The authors state that the mechanisms underlying interactions, and the distinction between adverse events due to toxicity and those caused by herb-drug interactions, present a significant challenge to future research.

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