Systematic review: hepatotoxic events associated with herbal medicinal products

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CRD summary
This review found some evidence that some herbal medicine products are associated with serious hepatotoxicity (liver damage). The authors stated that the incidence of events is generally unknown, and in most cases it could not be established that the herbal medicine caused the hepatotoxicity. The evidence presented appears to support the authors’ conclusions.

Authors’ objectives
To review recent reports of hepatotoxic events associated with the use of herbal medicine products (HMPs).

Searching
MEDLINE, EMBASE, the Cochrane Library, AMED and CISCOM were searched from 1990 until May 2002; the search terms were stated. The authors also handsearched relevant journals (unspecified) and their own files for additional published or unpublished reports. The bibliographies in all located papers were checked. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
The inclusion criteria were not specified in terms of study design. Case reports, case series and observational studies were included.

Specific interventions included in the review
Reports on the therapeutic use of HMPs were eligible for inclusion. Reports of accidental poisoning were excluded. The included studies reported on the use of a wide variety of HMPs.

Participants included in the review
The inclusion criteria were not specified in terms of participants. The participants in the included studies had been treated for a variety of conditions, such as skin conditions, gastrointestinal complaints, tumours, back pain, dysmenorrhea, meteorism, respiratory infections, asthma, weakness, obesity, high cholesterol, insomnia, anxiety, induction of abortion, healing of wounds and fractures, multiple sclerosis, hair loss, joint problems, urinary problems and other assorted problems. The included studies were of men, women and children.

Outcomes assessed in the review
Studies presenting data on hepatotoxic events that occurred from 1990 onwards were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently selected the studies for inclusion and resolved any disagreements on inclusion through discussion.

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

Data extraction
Two reviewers independently extracted the data and resolved any disagreements through discussion. The data extracted included: the age, gender and number of patients; specific herbal medicine and dose; the condition HMP was being used to treat; suspected toxic constituent; other medications; and the results of positive challenge alcohol
Methods of synthesis
How were the studies combined?
The studies were grouped according to the HMP and a narrative synthesis was undertaken.

How were differences between studies investigated?
Differences between the studies were not discussed.

Results of the review
Information from 52 case reports and case series of clinical data (n=153) were tabulated in the paper. Additional studies (including two observational studies with over 2,000 patients) were also mentioned in the text.

The authors stated that largely anecdotal and poorly reported evidence was found.

The following HMPs were reported to be associated with hepatotoxic events: Aristolochia (1 case); Bajiaoloan (5 cases reported in 1 case series); Cascara sagrada (1 case); Celandine (10 cases reported in 1 case series plus 1 case report); Chaparral (16 cases in one report); Germander (6 cases verified as occurring after 1990 in 1 case series plus 7 cases in 5 other reports); Jin Bu Huan (at least 11 cases); Kava (68 suspected cases including 14 classified as probable); Ma huang (at least 3 cases); Pennyroyal (1 case after 1990 reported in 1 series); Pyrrolizidine-containing HMPs (20 cases suspected of being due to traditional South African medicines, 4 of these cases had pyrrolizidine alkaloids in their urine); Senna (1 case report); and Skullcap (1 possible case and 1 case report).

Chinese herbal mixtures: 2 cases of hepatotoxicity were associated with a herbal remedy called ‘eternal life’, 12 cases were associated with skin treatments and 2 cases were associated with Shou-Wu-Pian. One observational study found that 1% (of 1,507) patients treated with Chinese herbal mixtures had clinically relevant elevations of liver enzyme levels. Another prospective observational study found that 8.5% (of 1,265) patients with normal baseline levels developed raised alanine transferase levels after taking Chinese medicines.

Kampo medicines: 2 cases of hepatotoxicity were associated with Dai-saiko-to and one case was associated with Saiko-keishi-kankyo-to.

Other herbal mixtures: one case of hepatotoxicity was associated with Euphytose; other cases have been reported to be associated with valerian plus skullcap, chaparral leaf containing tea, Isabgol, Prostata and Venencapsan.

Authors’ conclusions
Several HMPs are associated with serious hepatotoxicity. The incidence of events is generally unknown, and in most cases it could not be established that the herbal medicine caused the hepatotoxicity.

CRD commentary
The review question was clear in terms of the intervention and outcomes. Given the aim of the review, the lack of explicit inclusion criteria for the study design appears to have been reasonable. Several relevant sources were searched, the search terms were stated, no language restrictions were applied, and attempts were made to locate unpublished material. However, no details were given of the journals that were handsearched. Two reviewers independently selected the studies and extracted the data, which reduces the potential for bias and errors.

Relevant data on some of the included studies were tabulated, while additional studies were described in the text of the review. Validity was not formally assessed, although the authors did comment on some of the limitations of the evidence: the incompleteness of the data reported, the inability to estimate incidence rates of hepatotoxicity, and the lack of evidence in reports of a causal relationship between HMP and toxicity. The studies were appropriately combined in a narrative. The evidence presented appears to support the authors’ conclusions.
Implications of the review for practice and research
Practice: The authors stated that patients and health professionals should be educated about HMPs, and that health care professionals should be vigilant.

Research: The authors stated that there is a need for systematic research into HMPs.

Funding
Hepatitis C Trust, UK.

Bibliographic details

PubMedID
12950418

Indexing Status
Subject indexing assigned by NLM

MeSH
Drug-Induced Liver Injury; Humans; Phytotherapy /adverse effects; Plant Preparations /adverse effects; Plants, Medicinal /adverse effects

AccessionNumber
12003001963

Date bibliographic record published
31/12/2004

Date abstract record published
31/12/2004

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.