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Review

Characterizing the human equivalent dose of herbal medicines in animal toxicity studies ☆

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ABSTRACT

Ethnopharmacological relevance: Herbal medicines have been generally believed to be safe. With the increasing use of herbal medicine worldwide, however, the safety of traditional herbal drugs frequently becomes a medical issue.
Aim of the study: This study was aimed to characterize the safe dose of herbal medicines through the systematic review for "human equivalent dose (HED)" from animal-based toxicity studies.
Methods and materials: A literature search for animal-based toxicity studies of herbal medicines in eight databases, including PubMed and Embase, was performed without language restriction. From the "no observed adverse effect level (NOAEL)" of each animal study, HED values were then calculated according to the composition (single or multiple herbs) and indication of the medicines.
Results: Among 729 relevant articles identified in the initial screening, 112 (233 studies comprising 105 single-herb and 128 multiple-herb studies) that met our inclusion criteria were finally reviewed. The total average HED value (from mouse, rat, rabbit and dog) was 278.1 ± 358.0 mg/kg, and the values for single- and multiple-herb studies were 322.7 ± 488.4 mg/kg and 241.5 ± 189.2 mg/kg, respectively. When the studies were analyzed according to herbal drug indication, drugs used for revitalization had the highest HED value (433.0 ± 265.2 mg/kg), while those for infectious diseases had the lowest (110.6 ± 118.6 mg/kg).
Conclusions: Our results provide important information regarding the safe dose of herbal medicines; thus, these data offer researchers and practitioners information critical for drug development or clinical application.

Contents

☆The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/Xn5WH3

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1. Introduction

The World Health Organization (WHO) has reported that approximately three-quarters of the world's population use herbal medicines for their healthcare (Gilani and Rahman, 2005). The market for herbal medicines is continuously expanding worldwide, and comprised US $83 billion globally in 2012 (WHO, 2013). The safety and efficacy of herbal products have been guaranteed usually based on their long history of clinical application (Neergheen-Bhujun, 2013). However, increasing concern exists regarding the lack of scientific evidence for the safety and efficacy of herbal medicines. Recently, several studies have warned of the possibility of herbal-drug-associated toxicity (Raynor et al., 2011; Posadzki et al., 2013).

Along with the attention paid to the safety of herbal medicines, the number of toxicity studies of herbal medicines is increasing (Kim et al., 2013). However, the number of toxicity studies is lacking, and several have presented controversial data. In Korea, for example, one study indicated herbal medicines as the major cause of drug-induced liver disease (Suk et al., 2012); however, another prospective study reported clinical data that suggested the safety of herbal medicines (Jeong et al., 2012). Information regarding the incidence and mechanism of herbal toxicity remains vague (Bent, 2008). Herbal drug-associated toxicity could have multiple causes, including direct toxic effects of the herb, environmental factors, and the genetic background of subjects (Haller et al., 2002).

To clarify the toxic effects of herbal medicines, the epidemiology of herbal-drug toxicity and its risk factors should be scientifically investigated. Nonetheless, toxicity studies of herbal medicines have been often neglected due to the perception that herbal agents are safe because they are natural products and have a long history of use (Ye and He, 2010). The pharmacological and toxicological processes are usually based on animal studies and clinical evaluation (Afolabi et al., 2012). Animal toxicity studies are important for predicting side effects and deciding the safe dose of drugs before clinical studies (Ali et al., 2012); thus, animal toxicity studies are the "gold standard" for toxicity assessment (de Broe and Porter, 2008).

In animal toxicity studies, accessing the "no observed adverse effect level (NOAEL)" is a fundamental process (Dorato and Engelhardt, 2005). The NOAEL value indicates the highest dose level not producing a significant increase in adverse effects in the experimental animal. From the NOAEL value, the human equivalent dose (HED) and maximum recommending starting dose (MRSD) can be calculated; these provide core information regarding the safety range and toxic potential of certain clinical doses of drugs, including herbal products (FDA Guidance, 2005).

Many animal toxicity studies for herbal plants or herbal formula were conducted to date, however no investigation showing the overview of those data was done yet. This study aimed to characterize the NOAEL and HED values of herbal medicines through a systematic survey of toxicity studies conducted to date worldwide.

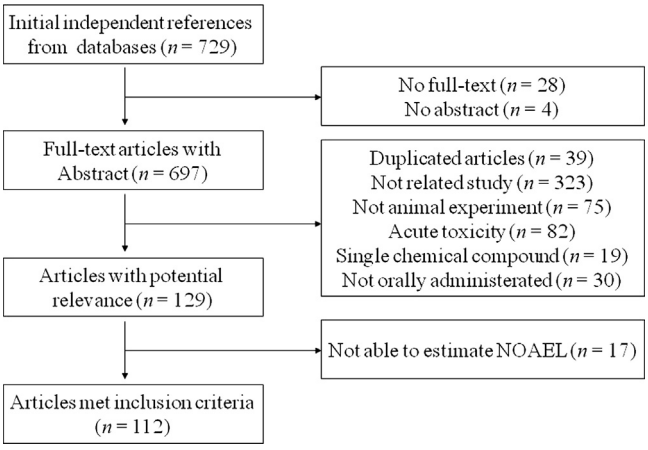

Fig. 1. Schematic of the data selection process.

2. Methods and materials

2.1. Data sources and key words

We searched the following eight databases: PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (www.embase.com/), KISS (http://kiss.kstudy.com/), RISS (http://www.riss.kr/), KISTI (http://www.kisti.re.kr/), National Assembly Library (http://www.nanet.go.kr/), OASIS (http://oasis.kiom.re.kr/), and KMbase (http://kmbase.medric.or.kr/) from their inception to January 31, 2014. Search terms comprised combinations of the following keywords: "herbal," "plant," "safety," "toxicity," "hepatotoxicity," and "NOAEL." No limitation of article type, publication status, or language (if an abstract is written in English) was imposed. Korean terms adopted from the above were retrieved from Korean databases.

2.2. Eligibility criteria

Articles were screened using the following inclusion criteria: (1) animal study, (2) toxicity study, (3) herbal resource, (4) oral administration of sample, and (5) articles that can estimate NOAEL. The exclusion criteria were as follows: (1) article without the full text or abstract, (2) article concerning other aspects such as an efficacy or a carcinogenicity study, (3) human study or review article, (4) acute toxicity or in vitro study, (5) single chemical compound, and (6) other route except oral administration. In addition, studies that cannot estimate NOAEL were excluded.

The title and abstract of each searched article was initially read by two authors simultaneously. Four authors decided the articles that met the inclusion criteria.

2.3. Data extraction and summarization

The authors thoroughly read the selected articles and extracted data regarding the type of herbal medicine (single or multiple herbs), species and gender of animal, treatment period, name of herb and clinical indication, and dose of sample, to calculate NOAEL value. Toxicity tests were classified as sub-acute (two to five weeks), sub-chronic (over 5–14 weeks) and chronic (over six months) according to the regulatory guidelines of various international organizations (Prieto et al., 2006). We counted male and female studies individually and each type of study when more than two were reported by a single article.