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Review

Assessment of herbal medicinal products: Challenges, and opportunities to increase the knowledge base for safety assessment

Scott A. Jordan [a,*], David G. Cunningham [a], Robin J. Marles [b]

[a] Marketed Biologicals, Biotechnology and Natural Health Products Bureau, Marketed Health Products Directorate, Health Canada, 200 Tunney's Pasture Driveway, Postal Locator 0701 A, Ottawa, Ontario, Canada K1A 0K9
[b] Bureau of Clinical Trials and Health Sciences, Natural Health Products Directorate, Health Canada

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ABSTRACT

Although herbal medicinal products (HMP) have been perceived by the public as relatively low risk, there has been more recognition of the potential risks associated with this type of product as the use of HMPs increases. Potential harm can occur via inherent toxicity of herbs, as well as from contamination, adulteration, plant misidentification, and interactions with other herbal products or pharmaceutical drugs. Regulatory safety assessment for HMPs relies on both the assessment of cases of adverse reactions and the review of published toxicity information. However, the conduct of such an integrated investigation has many challenges in terms of the quantity and quality of information. Adverse reactions are under-reported, product quality may be less than ideal, herbs have a complex composition and there is lack of information on the toxicity of medicinal herbs or their constituents. Nevertheless, opportunities exist to capitalise on newer information to increase the current body of scientific evidence. Novel sources of information are reviewed, such as the use of poison control data to augment adverse reaction information from national pharmacovigilance databases, and the use of more recent toxicological assessment techniques such as predictive toxicology and omics. The integration of all available information can reduce the uncertainty in decision making with respect to herbal medicinal products. The example of *Aristolochia* and aristolochic acids is used to highlight the challenges related to safety assessment, and the opportunities that exist to more accurately elucidate the toxicity of herbal medicines.

Contents

Abbreviations: AA, aristolochic acid; AAN, aristolochic acid nephropathy; AR, adverse reaction; DEG, differentially expressed gene; DES, diethylstilbestrol; GMP, good manufacturing practices; cGMP, current good manufacturing practices; HCP, healthcare practitioner; HMP, herbal medicinal product; MAH, market authorisation holder; NTP, National Toxicology Program; PCC, poison control centre; QSAR, quantitative structure activity relationship; TCM, traditional Chinese medicine.

* Corresponding author. Fax: +1 613 954 2354.
E-mail address: scott.jordan@hc-sc.gc.ca (S.A. Jordan).

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Introduction

Herbal medicinal products (HMPs) are widely used around the world, increasingly so in Western nations. A survey conducted in 2005 revealed that 71% of Canadians were using natural health products, a term which includes not only HMPs but also vitamins and minerals. In this study, 11% of the persons surveyed used herbal remedies and algal/fungal products (IPSOS Reid, 2005). In the United States, about 19% of the adult population were using HMPs as of 2002 (Kennedy, 2005). Another study has shown about 36% of pregnant women in Norway use herbs (Nordeng and Havnen, 2004).

Although HMPs are widely considered to be of lower risk compared with synthetic drugs, they are not completely free from the possibility of toxicity or other adverse effects (De Smet, 2004). High profile issues such as adverse reactions associated with *Ephedra* and *Aristolochia* have shown that HMPs can produce toxicity in humans. While inherent toxicity of certain herbs is well known, adverse effects from the use of HMPs may also result from contamination of products with toxic metals, adulteration with pharmacologically active synthetic compounds, misidentification or substitution of herbal ingredients, or improperly processed or prepared products (Ernst, 2004, Van Breemen et al., 2008, Ankli et al., 2008; Chan, 2009). Interactions may also occur between drugs, foods and other HMPs taken concomitantly (Foster et al., 2005, Fugh-Berman, 2000, Goldman et al., 2008).

Recently, there has been increased discussion on the safety assessment of herbs. Protocols and guidance documents on safety and toxicity testing of HMPs have been issued by the International Life Sciences Institute (summarised by Schilter et al., 2003), the Institute of Medicine / National Research Council (2004), the Union of Pure and Applied Chemistry (Mosihuzzaman and Choudhary, 2008), the European Medicines Agency (EMEA) (e.g. EMEA, 2007, 2009), and most recently by the European Food Safety Authority (EFSA, 2009). These guidance documents discuss the assessment of the safety of herbs for use in both foods and medicines. The types of testing described in these guidance documents represent the ideal type of information that could be obtained in order to adequately characterise the toxicity of a specific herb or a finished herbal product ready for the marketplace.

International regulatory systems for HMPs can be quite variable in terms of safety and toxicity testing requirements. In countries where HMPs are less strictly regulated than synthetic drugs, and where limited toxicity testing is required, or where HMPs are regulated as intermediate products classified separately from foods and drugs, where less stringent requirements exist for certain sub-types of products (e.g. traditionally used herbs where their long-term use is considered evidence for safety), pre-market assessment may be based on limited information.

Even in countries where HMPs are assessed in detail before market authorisation is given, pharmacovigilance is a critical activity to promote the safe use of HMPs throughout their life cycle. As the use of HMPs grows around the world, the identification of safety signals becomes of increased importance. The identification and investigation of safety signals associated with HMPs are subject to the same challenges as signals arising from pharmaceutical drugs. There are, however, challenges unique to HMPs. There are often deficiencies in both the quantity of information (e.g. under-reporting of adverse reactions, general lack of toxicological information on herbs) and the quality of information (e.g. poor quality of adverse reaction case reports or lack of information on the quality of HMPs associated with case reports submitted to regulatory authorities or published in the scientific literature). These factors present challenges when signals of safety concerns arise.

In the regulatory context, safety assessment can have bearing on whether certain products should be restricted, removed from the market, or have augmented safety information placed on labelling. In instances where little toxicity information exists on a specific herbal product or its ingredients, regulatory decisions on risk mitigation activities are likely to take a cautious approach, until further information is obtained which can potentially clarify the toxicity of the product, and reduce uncertainty in the risk assessment of HMPs.

This paper discusses the challenges which are faced in the assessment of safety of HMPs. Also discussed is the need for careful consideration of existing data, and opportunities for increasing both the quantity and quality of knowledge. From the post-market perspective, an integrative approach is necessary to investigate safety signals for any product type. Clinical assessment of adverse reaction reports, either submitted to the regulatory authority, or published in the scientific literature, needs to be considered along with available toxicological and pharmacological information in order to fully characterise potential safety concerns. While challenges exist for the assessment of HMP safety, efforts are being made to add quality information to the herbal safety knowledge base so that judgements on the hazard and risk of HMPs can be made with increased certainty.

Regulation of herbal medicinal products internationally

A regulatory framework for HMPs provides consumers greater assurance that the identities of medicinal ingredients have been verified, that they have been properly quantified per unit dose, that there has been an assessment of the safety and efficacy of the product