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Review article

Sources, distribution, bioavailability, toxicity, and risk assessment of heavy metal(loid)s in complementary medicines

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ABSTRACT

The last few decades have seen the rise of alternative medical approaches including the use of herbal supplements, natural products, and traditional medicines, which are collectively known as 'Complementary medicines'. However, there are increasing concerns on the safety and health benefits of these medicines. One of the main hazards with the use of complementary medicines is the presence of heavy metal(loid)s such as arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg). This review deals with the characteristics of complementary medicines in terms of heavy metal(loid)s sources, distribution, bioavailability, toxicity, and human risk assessment. The heavy metal(loid)s in these medicines are derived from uptake by medicinal plants, cross-contamination during processing, and therapeutic input of metal(loid)s. This paper discusses the distribution of heavy metal(loid)s in these medicines, in terms of their nature, concentration, and speciation. The importance of determining bioavailability towards human health risk assessment was emphasized by the need to estimate daily intake of heavy metal(loid)s in complementary medicines. The review ends with selected case studies of heavy metal(loid) toxicity from complementary medicines with specific reference to As, Cd, Pb, and Hg. The future research opportunities mentioned in the conclusion of review will help researchers to explore new avenues, methodologies, and approaches to the issue of heavy metal(loid)s in complementary medicines, thereby generating new regulations and proposing fresh approach towards safe use of these medicines.

"If we don't know what's in them (complementary medicines), it's very difficult to predict the interactions, …, the potential outcomes there are very serious".

Dr. Garth Maker, Murdoch University, Australia

1. Introduction

Complementary medicines (CM) are also known as traditional, natural, or alternative medicines, and include herbal medicines, vitamin and dietary health supplements, and traditional Ayurvedic (Sanskrit word meaning the "science of life"), Chinese, and homoeopathic medicines. Globally, self-prescribed vitamins, herbal medicines, and mineral supplements are the most common CM products used (Bodeker and Burford, 2007; WHO, 2005). For example, the number of assorted dietary supplements has risen to around 55,000 in the USA, with an estimated 60%, 50%, and 71% of Americans, Europeans, and Canadians using health supplements, respectively (Genuis et al., 2012). Over the past two decades, use of CM products has increased dramatically with an annual estimated US$0.7, $1.31, $7.18, and $33.9

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billions spent on these products in Australia, England, Canada, and the USA, respectively (CMA, 2012; WHO, 2005). Australia's *per capita* usage of CM products is considered to be among the highest in the world. Around 74% of the population use some form of CM products including vitamin, mineral, herbal, or nutritional supplements (CMA, 2012; Wootton, 2005). Recently, the use of CM products increased exponentially with annual global and Australian estimated market values at about $1.2 and $83 billion, respectively (ANAO, 2012; CMA, 2012; Xue et al., 2007). The global consumption of medicinal plants was about $14 billion *per annum* in 2005, which will be projected to increase to $5 trillion in 2050 (Rai et al., 2005).

Although the intent of using CM products is to gain health benefits, there is limited evidence on the effectiveness of many of these products (Bodeker and Burford, 2007; Genuis et al., 2012). While most CM products are of low risk, some traditional herbal and Ayurvedic formulations may need to be taken with caution as they contribute to Toxicity resulting from contaminants (Lynch and Braithwaite, 2005). Most risks associated with CM products result from contaminants that include pesticide residues and heavy metal(loid)s. Heavy metal(loid)s include both biologically essential (*e.g.*, cobalt (Co), copper (Cu), chromium (Cr), manganese (Mn), nickel (Ni), selenium (Se), and zinc (Zn)) and non-essential (*e.g.*, arsenic (As), cadmium (Cd), lead (Pb), and mercury (Hg)) elements (Adriano, 2001). The most common heavy metal(loid)s implicated in human toxicity include Pb, Hg, As, and Cd, although beryllium (Be), Mn, aluminium (Al), and Co may also cause toxicity.

Although most CM products may have health benefits, over recent years, increasing incidences of heavy metal(loid) toxicity following the use of these products have been reported (Bensoussan and Myers, 1996; Breeher et al., 2013; Gunturu et al., 2011; Lin et al., 2013). Most countries regulate the distribution and use of CM products. For example, the Australian Therapeutic Goods Administration (TGA) regulates CM products, including herbal, traditional Chinese or Ayurvedic medicines, if they are manufactured in Australia (TGA, 2016). Commercial importation of herbal medications also requires licensing and assessment through the TGA (Harvey et al., 2008). Similarly, several other countries regulate the distribution and use of CM products and have adopted guidelines for metal(loid)s in these products (Shia et al., 2007). Effective strategies to minimise or eliminate this risk are challenging for policy makers, but critical for optimising health.

This review aims to examine the impact of heavy metal(loid) contamination on the safety and toxicity of CM products, in relation to the distribution and bioavailability of metal(loid)s in these products. The review first discusses the sources, concentration, and distribution of heavy metal(loid)s in various CM products. Then, the toxicity of these heavy metal(loid)s in CM products will be examined in relation to bioavailability and bioaccessibility for human health. The practical implications of CM-borne heavy metal(loid)s on human health are discussed in relation to management guidelines for the safe and beneficial use of these products (Fig. 1).

2. Sources of heavy metal(loid)s in complementary medicines

Heavy metal(loid)s in CM products result from contamination during cultivation of plants used for CM products, contamination during processing, and the addition of heavy metal(loid)s as a therapeutic agent (Ang and Lee, 2007; Chan, 2003; Nagarajan et al., 2014a, 2014b; Table 1).

2.1. Heavy metal(loid) uptake by herbal plants

Accumulation of heavy metal(loid)s by herbal plants can occur through cultivation of these plants in contaminated soils, addition of heavy metal(loid)-enriched organic amendments including manure and compost as a nutrient source, and irrigation of herbal plants with wastewater sources containing heavy metal(loid)s (Table SI 1).

There has been an increasing tendency to use marginal and contaminated soils for the cultivation of non-edible crops such as fiber crops and energy crops, and also herbal plants for the synthesis of CM products (Chan, 2003; Sarma et al., 2011; Tripathi et al., 2012). Some of the herbal plants tend to accumulate heavy metal(loid)s when they are grown in contaminated soils. For example, Tripathi et al. (2012) noticed As uptake by native plants including medicinal plants in As-contaminated paddy fields. Similarly, Ramirez-Andreotta et al. (2013) monitored As accumulation in a range of plant species grown in mining-affected soils near Hambold smelter site in southern Arizona. Although As concentration was less in medicinal than in non-medicinal species, it was higher than the World Health Organisation (WHO) permissible level (WHO, 2011). However, Zheljazkov et al. (2008) demonstrated that three essential oil species *Marrubium vulgare* L. (white horehound), *Melissa officinalis* L. (lemon balm), and *Origanum heracleoticum* L. (oregano) did not remove significant amounts of heavy metal(loid)s and hence were able to be cultivated in metal(loid) polluted smelter soils as high-value crops. Rai et al. (2005) noticed that Cd concentration in *Phyllanthus amarus* (gale of the wind) used in the most popular Ayurvedic formulation (Chywanprash) increased with increasing Cd contamination in soil.

Baranowska et al. (2002) evaluated the level of five heavy metal (loid)s [Pb, Zn, Cd, Ni, and molybdenum (Mo)] in six medicinal plants [*Matricaria chamomilla* (chamomile), *Mentha rotundifolia* (mint), *Rosa rubiginosa* (briar), *Taraxacum ceratophorum* (dandelion), *Urtica dioica* (nettle), and *Hypericum perforatum* (St. John's wort)] from different heavily polluted locations and concluded that the concentrations of all the metal(loid)s were higher in plants collected from express highways, railway stations, and urban roads. Annan et al. (2013) studied the amount of Pb, Cd, Al, Hg, and As in 10 common medicinal plants and concluded that same species of medicinal plants, growing in different environments, accumulates different levels of these heavy metal(loid)s.

Since most of the herbal plants are used for natural remedy, these are grown organically using natural nutrient sources such as phosphate rocks, composts, and animal manures. Some of these sources are rich in heavy metal(loid)s, which are taken up by plants (Sarma et al., 2011). The use of treated wastewater to grow non-edible industrial crops including herbal plants to synthesize aromatic oils is increasing. For example, Khalifa et al. (2011) have demonstrated that wastewater irrigation increased the uptake of heavy metal(loid)s in a number of aromatic plants although low levels of toxic elements were noticed in the volatile oils of these plants. Similarly, Lal et al. (2013) noticed that Cd, Cr, Ni, and Pb concentrations in lemon grass (*Cymbopogon flexuosus*) were higher in recycled water than with groundwater irrigation.

2.2. Cross-contamination during processing

Cross contamination of heavy metal(loid)s may occur during the processing and preparation of CM products (Flegal et al., 2013; Mahapatra and Nguyen, 2007). For instance, Sullivan et al. (2010) indicated that heavy metal(loid)s may enter into herbal products through bioaccumulation from the harvest site and during postharvest processing phases, such as drying, grinding, and solvent extraction. The elevated Pb concentrations of many of the Chinese herbal supplements have often been attributed to external contamination from drying and manufacturing (Flegal et al., 2013; Wang et al., 1999). During the preparation of a herbo-mineral drug, Dhundi et al. (2012) noticed the presence of Pb in their samples, which they attributed to cross-contamination from adjacent formulations or Pb-enriched water used for washing.

Processing of herbal plants for producing herbal medicines can impact the redistribution of heavy metal(loid)s. For example, Abou-Arab and Abou Donia (2000) noticed that boiling the plants in water extracted greater amounts of metal(loid) than immersing in hot water, indicating that the heavy metal(loid) contamination of the end product can be managed by the extraction process. Ting et al. (2013) evaluated