Journal of Ethnopharmacology 210 (2018) 340–350

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

journal homepage: www.elsevier.com/locate/jethpharm

Review

A review of cinnabar (HgS) and/or realgar (As_4S_4)-containing traditional medicines

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ARTICLE INFO

Keywords:
Herbo-metallic preparations
Cinnabar
Realgar
Zuotai
Arsenic
Mercury
Disposition
Efficacy
Safety evaluation

ABSTRACT

Ethnopharmacological relevance: Herbo-metallic preparations have a long history in the treatment of diseases, and are still used today for refractory diseases, as adjuncts to standard therapy, or for economic reasons in developing countries.

Aim of the review: This review uses cinnabar (HgS) and realgar (As_4S_4) as mineral examples to discuss their occurrence, therapeutic use, pharmacology, toxicity in traditional medicine mixtures, and research perspectives.

Materials and methods: A literature search on cinnabar and realgar from PubMed, Chinese pharmacopeia, Google and other sources was carried out. Traditional medicines containing both cinnabar and realgar (An-Gong-Niu-Huang Wan, Hua-Feng-Dan); mainly cinnabar (Zhu-Sha-An-Shen Wan; Zuotai and Dangzuo), and mainly realgar (Huang-Dai Pian; Liu-Shen Wan; Niu-Huang-Jie-Du) are discussed.

Results: Both cinnabar and realgar used in traditional medicines are subjected to special preparation procedures to remove impurities. Metals in these traditional medicines are in the sulfide forms which are different from environmental mercurials ($HgCl_2$, MeHg) or arsenicals ($NaAsO_2$, NaH_2AsO_4). Cinnabar and/or realgar are seldom used alone, but rather as mixtures with herbs and/or animal products in traditional medicines. Advanced technologies are now used to characterize these preparations. The bioaccessibility, absorption, distribution, metabolism and elimination of these herbo-metallic preparations are different from environmental metals. The rationale of including metals in traditional remedies and their interactions with drugs need to be justified. At higher therapeutic doses, balance of the benefits and risks is critical. Surveillance of patients using these herbo-metallic preparations is desired.

Conclusion: Chemical forms of mercury and arsenic are a major determinant of their disposition, efficacy and toxicity, and the use of total Hg and As alone for risk assessment of metals in traditional medicines is insufficient.

1. Introduction

Minerals exist naturally in the environment. In the periodic table, over 75% of the elements are metals and eight are metalloids. People are exposed to minerals through the food we eat, the water we drink, and the polluted air we breathe, as well as the medicines we take. Nine metals are essential to human health such as zinc (Zn), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), selenium (Se), cobalt (Co) and trivalent chromium (Cr). Any deficiency, excess or imbalance of essential metals in human body may lead to metabolic disorders. The metals of major toxicological concern are lead (Pb), cadmium (Cd), mercury (Hg), nickel (Ni) and the metalloid arsenic (As). The majority of metals belong to minor toxic metals such as silver (Ag), tin (Sn), etc. (Liu et al., 2008c). Minerals are also used in medicines such as the well-known platinum (Pt) derived anticancer drugs, lithium carbonate as antimanics, aluminum hydroxide as antacids, as well as the herbo-metallic preparations used in traditional medicines.

Abbreviations: AGNH, An-Gong-Niu-Huang Wan; HFD, Hua-Feng-Dan; ZSASW, Zhu-Sha-An-Shen Wan; HDP, Huang-Dai-Pian, Realgar-Indigo Naturalis; LSW, Liu-Shen-Wan; NHJD, Niu-Huang-Jie-Du Pian

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http://dx.doi.org/10.1016/j.jep.2017.08.037
Received 24 June 2017; Received in revised form 27 August 2017; Accepted 28 August 2017
Available online 31 August 2017
0378-8741/

Minerals have been used in traditional medicines since ancient times, and are still in use today. In traditional Indian medicine Ayurveda, 8% of the recipes contain 15 kinds of minerals (metals) altogether (Joshi et al., 2017). In traditional Chinese medicines, minerals are ingredients used to assist the presumed therapeutic effects. For example, in the 2015 edition of the Pharmacopeia of China (Vol 1), at least 10 minerals are listed in the 1493 traditional recipes, approximately 7% of the recipes contain cinnabar and/or realgar (Pharmacopoeia of China, 2015). In traditional Tamil system of Siddha Medicine, nearly half of the preparations used for diabetes treatments contain inorganics, including cinnabar and realgar (Sathasivampillai et al., 2017). In traditional medicines used in Sri Lanka, minerals including cinnabar are found (Kankanamalage et al., 2014). Among the minerals used in traditional remedies, cinnabar (96% HgS) and realgar (90% As_4S_4) have received the most public concerns of their safety (Liu et al., 2008a, 2008b; Wang et al., 2015c), and will be the focus of this minireview.

It should be noted that only sulfide forms of mercury and arsenic are used in oral traditional medicines. "Rasasindura" is primarily composed of mercuric sulfide (HgS) and has been used in Indian Ayurvedic medicines for treatment of chronic ailments, such as syphilis, high fever, pneumonia, insomnia, nervous disorders, and paralysis of the tongue (Kamath et al., 2012). In Tibetan medicines, mercury sulfides (α-HgS or β-HgS) are frequently included in the herbo-metallic preparations for the treatment of stroke, brain trauma, neuroinflammation, and chronic ailments (Chen et al., 2012; Kan, 2013; Huang et al., 2013). Realgar (also called Xionghuang) was used in the treatment of various diseases, including headache, vertigo, sore throat, mouth ulcers, tongue ulcers, but most importantly, realgar shows promising anticancer activity in combination with other medications (Wang et al., 2008; Zhang et al., 2009; Wu et al., 2011a). Cinnabar (also called Zhusha) is a key sedative component in many Chinese medicines (Zhou et al., 2009). However, both mercury and arsenic are known toxic metal/metalloids. How to evaluate their safety and balance their benefits and risks represents a challenge to the scientific community. This article provides a minireview of the seven commonly used cinnabar- and/or realgar-containing medicines, from the history, clinical use, pharmacology and toxicology, in general to their benefits and risks, as well as the research perspectives.

2. Cinnabar and realgar differ from environmental mercurials and arsenicals

Cinnabar (α-HgS) and metacinnabar (β-HgS) are structurally different from mercury chloride ($HgCl_2$) and methylmercury (MeHg), and are the only chemical form used in oral traditional remedies. Similarly, realgar (As_2S_2, As_4S_4) is structurally different from sodium arsenate (As^{5+}) and sodium arsenite (As^{3+}), and is the form used in oral traditional medicines (Fig. 1). The chemical forms of cinnabar and realgar are major determinants of their disposition, efficacy and toxicity.

In traditional Chinese medicines, cinnabar is subjected to grinding and washing (called Shui-Fei) at least 3–4 times to remove impurities, and this procedure is very important for the safe use of cinnabar in medication (Zhu et al., 2005; Pharmacopoeia of China, 2015). Zuotai (β-HgS, metacinnabar) undergoes the tedious processing procedures like Bhasmas in Ayurvedic medicine (Kamath et al., 2012), which usually takes months of repeated incineration and processing procedures using herbals and animal-based products (Chen et al., 2012; Kan, 2013). Similarly, realgar (As_4S_4) is also subjected to the Shui-Fei process, and after repeated grinding and washing with water, the impurities are removed, as revealed by X-ray diffraction analysis, showing that after purification of realgar by Shui-Fei, arsenic is in the form of α-AsS and β-As_4S_4, while the toxic form of As_2O_3 is removed (Cao et al., 2012).

When discussing mercury toxicity, three mercury forms (elementary mercury, inorganic mercury, and organic mercury) must be distinguished (Klaassen, 2006); similarly, arsenic sulfide is toxicologically quite different from arsenite and arsenate (Liu et al., 2008a). Thus, the sulfide forms of cinnabar and realgar are the basis of their therapeutic effects and safety after oral administration.

3. Cinnabar or realgar is seldom used alone but as polyherb-metallic mixtures

Minerals are not used alone in traditional remedies, rather as a mixture with herbs and/or animal-based products. In the mixture, chemical reactions may occur, and various ingredients are assumed to assist each other for the desired therapeutic effects and to reduce toxicity. Examples of cinnabar- and/or realgar-containing traditional medicines are given in Table 1.

The traditional medicines in Table 1 are grouped into three major categories, i.e., traditional medicines containing both cinnabar and realgar (AGNH, HFD); mainly mercury sulfides (ZSASW, Zuotai and Dangzuo); and mainly arsenic sulfides (HDP, LSW, NHJD). For each medicine, the clinical application will be introduced first, followed by toxicology studies, and the known pharmacology data will also be provided.

4. Traditional medicines that contain both cinnabar and realgar

4.1. An-Gong-Niu-Huang Wan (AGNH)

AGNH is a famous Chinese medicine used for brain emergencies (Lu et al., 2011a, 2011b, 2011c). It has over 300 years of drug history composed of 4 herbs (*Coptis chinensis* Franch; *Scutellaria baicalensis* Georgi; *Gardenia jasminoides* Ellis; *Curcuma wenyujin* Y.H.Chen & C.Ling), 4 animal-based products (*Bos taurus domesticus* Gmelin (Niuhuang, the gallstone of cow)); *Pteria martensii* (Ounker) (Zhenzhu); *Bubalus bubalis* Linnaeus (Shuiniujiao, in place of *Rhinoceros unicornis*); *Moschus berezovskii* Flerov (Shexiang, musk), and 3 minerals (cinnabar, realgar, and Borneolum Syntheticum). Cinnabar (10%) and realgar (10%) are major components of AGNH. It is still a popular medicine for brain emergencies such as brain trauma, bleeding, brain infection, ischemia and stroke (Pharmacopoeia of China, 2015). It is an over-the-counter drug available in many Chinese drug stores and can be found in Beijing Airport Tong-Ren-Tang Store.

Both mercury and arsenic are Class 1 elements of human toxicity that have limited or no use as drugs in Western societies. The Permitted Daily Exposure (PDE) of oral mercury (Hg) is 30 μg/day, and oral arsenic (As) is 15 μg/day (ICH, 2014). In the Pharmacopoeia of China (2015), the limit of Hg is 1 mg/kg and As is 5 mg/kg in crude herbal materials. AGNH contains 10% cinnabar and 10% realgar, and a pill (3 g) per day for a 60 kg person is 261 mg Hg/day and 210 mg As/day. Thus, the Hg and As contents in AGNH are thousands-fold higher than the usual allowable limit for Hg and As.

Advanced technology has been used to analyze the chemico-physiological properties of Hg and As in AGNH. For example, homogeneous blending of cinnabar and realgar is considered to be essential for good bioactivity of AGNH, and Laser-induced breakdown spectroscopy (LIBS) has been proposed to assess the blending end-point of AGNH (Liu et al., 2015). HPLC/ICP-MS analysis shows that methyl mercury, ethyl mercury and Hg^{2+} are not found in the extracts of AGNH (Wang et al., 2015b), but only trace soluble mercury in forms of $Hg_3S_2Cl_2$, $HgS_2(OH)^-$, and $HgS_3(OH)^-$ are found under simulated gastric and intestinal conditions (Zhou et al., 2010, 2011). Although the amount of Hg and As in AGNH is high, the chemical forms of metals are different from that of environmental mercurials and arsenicals.

To assess the potential toxicity of AGNH, in vitro and in vivo studies have been performed. In 5 different brain and liver cell lines incubated with AGNH, Hg and/or As compounds for 48 h, the cytotoxic concentration that killed 50% of the cells showed huge differences: AGNH extract was much less toxic than MeHg (1/300), $HgCl_2$ (1/30), As^{5+} (1/