Mineral arsenicals in traditional medicines: Orpiment, realgar, and arsenolite

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Abstract

Mineral arsenicals have long been used in traditional medicines for various diseases, yet arsenic can be highly toxic and carcinogenic. Arsenic in traditional medicines typically comes from deliberate addition for therapeutic purposes, mainly in the form of mineral arsenicals including orpiment (As_2S_3), realgar (As_4S_4), and arsenolite (contains arsenic trioxide, As_2O_3). Inorganic arsenic is now accepted in Western medicine as a first line chemotherapeutic agent against certain hematopoietic cancers. This minireview analyzes the pharmacology and toxicology of these arsenicals used in traditional medicines. Orpiment and realgar are less soluble and poorly absorbed from the gastrointestinal tract, while the bioavailability of arsenic trioxide is similar to inorganic arsenic salts like sodium arsenite. Pharmacological studies show that arsenic trioxide and realgar are effective against certain malignancies. Orpiment and realgar are used externally for various skin diseases. Realgar is frequently included as an ingredient in oral traditional remedies for its antipyretic, antiinflammatory, antiulcer, anticonvulsive and anti-schistosmiasis actions, but the pharmacological basis for this inclusion still remains to be fully justified. Toxicological studies show that cardiovascular toxicity is the major concern for arsenic trioxide, and the gastrointestinal and dermal adverse effects may occur after prolonged use of mineral arsenicals. Little is known about possible secondary cancers resulting from the long-term use of any of these arsenicals. Similar to the safety evaluation of seafood arsenicals, total arsenic content alone appears to be insufficient for mineral arsenical safety evaluation. Arsenic speciation, bioavailability, and toxicity/benefit should be considered in evaluation of mineral arsenical-containing traditional medicines.

Keywords

Arsenic; Traditional medicines; Orpiment; Realgar; Arsenolite; Cancer chemotherapy

Introduction

Traditional medicines, mainly Chinese medicines and Indian Ayurvedic medicines are becoming more and more popular as alternative and supplementary remedies over recent years (Efferth et al., 2007; Kumar et al., 2006). Toxic metals or metalloids such as lead, mercury, and arsenic are frequently found in traditional medicines, raising justifiably escalating public concerns (Ernst, 2002; Cooper et al., 2007). Indeed, at least for arsenicals, many traditional medicines call for intentional addition of mineral arsenicals based on their presumed or defined therapeutic properties (Ernst, 2002; Miller et al., 2002; Evens et al., 2004; Pharmacopeia of

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China, 2005; Efferth et al., 2007). However, arsenic is a known human carcinogen producing cancers of the skin, lung, urinary bladder, liver, kidney, and possibly other sites (NRC, 1999; IARC, 2004), and has many other profound toxic effects following acute or chronic exposure (NRC, 1999; ATSDR, 2005; Liu et al., 2007). The general perception is that intentional addition of a known carcinogen to any medicine is a preposterous risk. The conundrum is that arsenicals have a long and remarkable history of pharmacology utility. Nonetheless, arsenic used in traditional medicines alarms the public and this minireview will first assess the available database on mineral arsenicals in traditional medicines and then attempt to analyze their risk in light of their potential benefit.

Use of mineral arsenicals in traditional medicines

Arsenic has been used as a poison and as a therapeutic since ancient times (Miller et al., 2002; ATSDR, 2005; Liu et al., 2007). In ancient Chinese medicines, the use of arsenic can be traced back to 200 BC in *Shen Nong Ban Cao Jing*, the first traditional Chinese medicine book. Using a poison to attack another poison or to fight against malignant diseases is a common concept in traditional Chinese medicines (Evens et al., 2004; Pharmacopeia of China, 2005). The use of mineral elixir made from the "essence of the five planets" including arsenic-containing minerals was thought to give humans perpetual life in Indian Ayurvedic medicines (Kumar et al., 2006). Table 1 lists properties of the three major arsenic-containing minerals used in traditional medicines. These arsenicals include orpiment, which is also called yellow arsenic, *Arsenikon* (Greek) or *Cihuang* (China), and contains arsenic trisulfide (As_2S_3). Another is realgar, which is also called red arsenic due to a deep red color, or *Xionghuang* (China), and contains > 90% arsenic disulfide or tetra-arsenic tetra-sulfide (As_2S_2, As_4S_4). Arsenolite, which is the third common mineral arsenical called white arsenic, contains largely arsenic trioxide (As_2O_3). Physicians prescribed arsenicals for both external and internal use throughout the 19 century (Miller et al., 2002; Evens et al., 2004). Arsenic and arsenic salts were key ingredients in antiseptics, antispasmodics, hematinics, sedatives, ulcer and cancer cures. Arsenical preparations, such as Fowler solution (1% potassium arsenite), were used by many physicians in the treatment of malignant diseases such as leukemia, Hodgkin's disease and pernicious anemia as well as non-malignant diseases such as psoriasis, pemphigus, eczema, and asthma for centuries (Miller et al., 2002; Evens et al., 2004). Arsphenamine was the standard therapy for syphilis for nearly 40 years before it was replaced by penicillin. Approximately 60 different arsenic preparations have been developed and used during the lengthy pharmacological history of arsenic until their uses were gradually replaced by more effective and less toxic modern agents (Miller et al., 2002; Evens et al., 2004; Efferth et al., 2007). Today, hundreds of traditional Chinese medicines still use orpiment, realgar, or arsenolite, and realgar alone is included in 22 oral remedies based on Pharmacopeia of China (2005). In Indian Ayurvedic medicines, realgar is also a major component in *bhasmas* (Mitra et al., 2002; Kumar et al., 2006). Arsenic trioxide is now becoming a very promising chemotherapeutic agent in Western medicine to treat acute promyecytic leukemia (APL) and possibly other malignancies (Miller et al., 2002; Evens et al., 2004; Hede, 2007).

Arsenic species and their acute toxicity

Arsenic exists in the trivalent and pentavalent forms and is widely distributed in nature. The most common toxic inorganic arsenic compounds are sodium arsenate (As^{5+}) and sodium arsenite (As^{3+}). In the body, arsenate can be reduced to arsenite, followed by conjugative methylation reaction to form monomethylarsononous acid (MMA), then dimethylarsinic acid (DMA), and finally trimethylarsonic acid (TMA), with these methylated species found in urine (Figure 1A) (Liu et al., 2007). Arsenic toxicity is highly dependent on the chemical form and, where known, the acute oral LD_{50} values in rodents are also included under each arsenic compound in Figure 1. In general, sodium arsenate (LD_{50} 112-175 mg/kg) is 4-5 times less

acutely toxic than sodium arsenite (LD_{50} 15-44 mg/kg), and the pentavalent organic arsenicals MMA (LD_{50} 960 mg/kg), DMA (LD_{50} 650 mg/kg), and TMA (LD_{50} 10.6 g/kg) are 40-100 times less acutely toxic than arsenite (Kreppel et al., 1993; ATSDR, 2005). Arsenicals in seafood mainly exist as organic forms (Fig. 1B), such as arsenobetaine (LD_{50} 10 g/kg), arsenosugar (not available), and arsenocholine (LD_{50} 6.5 g/kg) (Borak et al., 2007), with acute oral LD_{50} values 100-500 fold above arsenite or arsenate. In traditional medicines, natural arsenic-containing minerals are used as drugs, such as orpiment, realgar, and arsenolite (Figure 1C). The oral LD_{50} for arsenic trioxide (i.e., arsenolite) in mice is 33-39 mg/kg (Carter et al., 2003), similar to sodium arsenite, but the LD_{50} for realgar is 3.2 g/kg, a difference of 100-fold compared to sodium arsenite (Zhang et al., 2004). The oral LD_{50} for orpiment is not available, possibly because orpiment is mainly for external use (Pharmacopeia of China, 2005). The wide range of LD_{50} values among different arsenicals clearly indicates that mineral arsenical toxicity is highly dependent on the chemical form.

Bioavailability of orpiment, realgar, and arsenolite/arsenic trioxide

It is generally assumed that the severity of poisoning is related to the total amount of poison ingested, and assessment of health risk associated with arsenic exposure from human ingestion of traditional medicines has typically taken this tactic (Ernst, 2002; Cooper et al., 2007). However, in many cases, a significant portion of some forms of mineral arsenicals are poorly absorbed into the body and would be unavailable to cause systemic damage. The disposition of these arsenicals in the body depends on various key factors including solubility, absorption, distribution and excretion. Table 2 lists the available data on disposition of these mineral arsenicals.

Orpiment has low solubility in water. Orpiment dissolution is kinetically slow and under anaerobic conditions, an increase in pH increases orpiment dissolution rate (Floroiu et al., 2004). For instance, in aqueous solution, more arsenic from orpiment is dissolved at pH 7 than pH 4 (Marafante and Vahter, 1987). When orpiment is incubated in a cell culture media, 3% of arsenic is released, which is actually decreased in the presence of pulmonary macrophages (Lantz et al., 1995). Macrophages engulf particles into phagosomes which have an acidic milieu (Floroiu et al., 2004). Orally administered orpiment is poorly absorbed, and over 82% is found in feces within 3 days, representing an unabsorbed portion of the dose, as compared to only 12% of an oral dose of sodium arsenate. Urinary arsenic metabolites from oral orpiment exposure are mainly DMA, suggesting that the biotransformation of absorbed orpiment arsenicals occurs in the body (Marafante and Vahter, 1987).

Realgar in *Niuhuang Jiedu Pian*, a common preparation for cold, has a low solubility in water, and only 4% is bioavailable in physiological gastric juice or intestinal fluid (Koch et al., 2007). The average total arsenic concentration in a *Niuhuang Jiedu Pian* is about $7 \pm 1\%$ (i.e., 70,000 ppm), corresponding to 28 mg arsenic per pill, of which only 1 mg arsenic finds its way into the blood stream, and 40% of this absorbed arsenic (0.4 mg) is excreted in urine (Koch et al., 2007). Realgar exposure results in various arsenical metabolites in the urine including MMA, DMA, arsenobetaine and an unknown metabolite, the level of which peaked at about 14 hours after ingestion (Koch et al., 2007). In healthy volunteers, <1% of total administered arsenic was found in the urine after repeated doses of *Niuhuang Jiedu Pian* (3 tablets, twice a day) during a 7 day period (Tang and Wang, 2005). Oral administration of realgar in rats (150 mg/kg, daily for 5 weeks) showed that only a small portion of arsenic was absorbed and reached the blood (45 mg/mL), lung (5.4 mg/g), spleen (5.2 mg/g) or liver (2.9 mg/g) (Tang and Wang, 2005). To overcome the low solubility and poor bioavailability, realgar nanoparticles have been prepared by cryo-grinding with polyvinylpyrrolidone and SDS, and arsenic solubility can greatly increased compared to crude realgar powder (Wu and Ho, 2007). Realgar nanoparticles show remarkable increases in bioavailability both *in vitro* and *in vivo*. For example, urinary

recovery of arsenic in rats after a single oral administration of realgar nanoparticles (50 mg/kg, po) was increased to 70% of the dose, as compared to 25% when realgar was given in crude powder (Wu and Ho, 2007).

Arsenic trioxide, purified from mineral arsenolite, is highly water soluble and well absorbed after oral dose. Thus, the oral LD_{50} in mice for arsenic trioxide is very close to that of sodium arsenite (Carter et al., 2003). Pharmacokinetic studies in humans show that after arsenic trioxide 10 mg/day, i.v. infusion for ~ 90 days for cancer chemotherapy, blood arsenite levels reached steady state of 5.5 – 7.3 mol/L (Shen et al., 1997). In another study, patients received repeated administrations of arsenic trioxide at similar doses and duration, plasma concentration of arsenic reached a stead-state after 4 weeks of treatment, and 60% of arsenic dose was excreted in urine in the forms of arsenite (14%), arsenate (7%), MMA (19%), and DMA (21%) (Fujisawa et al., 2007). Compared to i.v. administration, orally given arsenic trioxide can achieve similar mean plasma levels (Kumana et al., 2002), an indication of its high level of absorption from the gastrointestinal tract.

It is clear that solubility and bioavailability of orpiment and realgar are poor as compared to arsenic trioxide (i.e., arsenolite), but the preparation can have a major impact as seen with realgar (i.e., nanopaticles versus crude powder), and when realgar is included in traditional medicines its bioavailability can be affected by other herbal components. For example, the individual herbs in *Angong Niuhuang Wan* can reduce arsenic release from realgar by 25-55% (Tang and Wang, 2005). Absorbed arsenic from orpiment or realgar does appear in the blood, but with much less distribution to the tissues due to poor absorption. Arsenic from mineral arsenicals, once absorbed, can be acted upon to produce arsenical metabolites, including primarily DMA (Marafante and Vahter, 1987; Koch et al., 2007; Fujisawa et al., 2007). The bioavailability is a critical determinant of efficacy and toxicity of arsenical compounds. Thus, it is not surprising that realgar and orpiment have quite different toxicological profiles from arsenic trioxide.

Pharmacology of orpiment, realgar and arsenolite/arsenic trioxide

Mineral arsenicals have long history of therapeutic use in traditional medicines (Evens et al., 2004; Kumar et al., 2006; Efferth et al., 2007). Table 3 lists some examples of mineral arsenicals still used today in traditional remedies based on Pharmacopeia of China (2005).

Orpiment is mainly used externally as louse-killer, a cure for scabies, for snake bites, insect stings, and skin diseases (Pharmacopeia of China, 2005; Koch et al., 2007). Orpiment is included in *Quingyi Piwen Dan*, a preparation of detoxication and laxative use with other 74 herbs, but its use alone in oral remedies is not common. Nanoparticles of orpiment have been prepared, and they were effective in killing leukemia K562 cells in vitro (Lin et al., 2007). Additional study is required with these orpiment nanoparticles since the absorption of arsenic from nanoparticle preparations are greatly enhanced.

Realgar is widely used in the combination with traditional medicines for both external and internal uses based on Pharmacopeia of China (2005) and some examples are listed in Table 3. For example, the most common over-the-counter preparation *Niuhuang Jiedu Pain* contains 6.4% of realgar, and the bioavailability of arsenic released from this preparation is very low (Koch et al., 2007). The therapeutic uses of these preparations range widely, as, for instance, for common colds, toothache and tonsillitis, asthma, abdominal pains, spasms, sedation, ulcers, heatstroke, coma, and delirium. Few pharmacologic studies on these preparations are found in the English literature. The interactions of realgar with other herbs, or minerals, such as cinnabar (HgS), in many cases, are unknown. In this minireview only the anticancer effects of realgar are briefly discussed. To enhance therapeutic efficacy and reduce adverse effects, physicians

of traditional Chinese medicine prescribe the combination formulae of plant species/minerals, based on clinical experience, and thousands of such formulae have been recorded (Wang et al., 2008). For example, *Awei Huapi Gao*, a preparation containing 4% realgar, appears effective against "lumps" or various malignancies in traditional therapies. Since 1960s, realgar-containing preparations, such as *Fufan Qingdai Pian*, *Kebai Dan*, *Manli Pian*, etc., have been successfully used in the treatment of certain types of acute and chronic leukemia (Chen et al., 2000). When the realgar amount is doubled as in *Fufan Qingdai Pian*, a better antitumor response is achieved (Chen et al., 2000). Realgar is less toxic as compared to arsenic trioxide, and is now used alone or in combination for hematologic malignancies (Lu et al., 2002;Shen et al., 2004). Recently, Realgar-*Indigo naturalis* formulae have been shown to be very effective against promyelocytic leukemia (Wang et al., 2008). Realgar acts as the principal component of the formula, whereas other plant active ingredients (such as indirubin and trashinone IIA) serve as adjuvant ingredients, in inducing acute promyelocytic leukemia cell differentiation and the degradation/ubiquitination of promyelocytic leukemia-retinoic acid receptor-oncoprotein, in enhancing G_1/G_0 arrest in APL cells through hitting multiple targets, and in intensifying Aquaglyceroporin-9 expression and thus facilitating transportation of realgar into APL cells (Wang et al., 2008).

Arsenolite is traditionally used for removing "lump" or "scrofula", and is included in *Ailin Yihao* as a modification of Pharmacopeia of China in the treatment of acute promyeocytic leukemia (Shen et al., 1997; Chen et al., 2000). Arsenic trioxide is an example of how an active ingredient is identified, purified, and successfully used to treat cancers with stunning efficacy (Miller et al., 2002; Hede, 2007). This is indeed a remarkable story of where traditional and modern medicines intersected to provide a cure for a once deadly disease. Arsenic trioxide is currently a first line chemotherapeutic in Western medicine for the treatment of certain leukemias, particularly in the treatment of drug resistant and relapsed acute promyelocytic leukemia (Miller et al., 2002; Evens et al., 2004; Hede, 2007). In addition to the effective use for hematological malignancies, arsenic trioxide plus buthionine sulfoximine (BSO, a cellular GSH depleter) is also effective against solid tumor cells (Maeda et al., 2004). Arsenic trioxide is also effective against metastatic cervical cancers (Yu et al., 2007). New studies on chemotherapy with arsenic trioxide are under way (Hede, 2007).

In traditional medicine-based therapy, patient treatment commences without any experimental phase in the laboratory. The Western concept of "from bench to bedside" does not fit in clinical practice of traditional remedies (Efferth et al., 2007). Nonetheless, the pharmacological basis for mineral arsenical inclusion in traditional medicine still remains to be fully justified.

Toxicology of orpiment, realgar and arsenolite/arsenic trioxide

Arsenicals are known as *Poisons of the King* since ancient times, and it has a variety of acute and chronic toxic effects, such as skin lesions, vascular toxicity, respiratory, renal and liver toxicity, and most importantly the carcinogenic potential (ATSDR, 2005; IARC, 2004). The wide range of LD_{50} among mineral arsenicals (Figure 1) points towards the need to discuss the toxicology of mineral arsenicals individually (Table 4).

Intraperitoneal administration of orpiment was negative in mouse bone marrow cell micronuleus assay, despite the resultant very high blood arsenic levels (900 ng/mL) (Tinwell et al., 1991). Intratracheal administration of orpiment (3.75 mg/kg, once a week for 15 weeks) in hamsters did not increase lung tumor incidence (Yamamoto et al., 1987). No toxicity reports in humans were identified from the literature, but the toxic potential of orpiment is generally thought to be greater than realgar (Pharmacopeia of China, 2005).

Realgar is widely used externally and internally in combination with other traditional medicines. Many of these preparations are commercially available in drug stores without

prescription, and in general, they are safe with very few reports on their toxicities or adverse effects. However, skin lesions and dermal adverse effects are reported from the long-term use of realgar-containing medicines such as *Niuhuang Jiedu Pian* (Ernst, 2002; Wang et al., 2005). In humans chronically taking realgar-containing traditional medicines at higher doses, mild gastrointestinal discomfort may occur, but no myelosuppression is observed (Lu et al., 2002). The major concern for high dose and long-term realgar treatment in humans is cardiac toxicity, manifested as prolonged QT wave, which is a dose-dependent finding. However, this side effect is tolerable and reversible (Shen et al., 2004). Liver is a major target organ of chronic arsenic toxicity, and the long-term use of realgar in humans may cause fatty liver, but neither liver fibrosis nor dysfunction is observed (Qin et al., 2006). When realgar-containing Indian medicine *Swarnabhasma* (gold ash) was administered to mice for 8 weeks, no apparent chronic toxicity (as evidenced by serum aminotransferases, urea and creatine levels and histopathology) is evident (Mitra et al., 2002). However, the well-designed dose- and time-related toxicology studies are required to critically evaluate the toxicology profiles of realgar-containing traditional medicines.

Arsenic trioxide is highly toxic compared to orpiment and realgar. Acute toxicity of arsenic trioxide is the major concern in the use of this agent to against malignancies, and at least three sudden deaths have been reported (Westervelt et al., 2001). Prompt chelation treatment is beneficial for acute arsenic trioxide intoxication, and a potentially lethal case taken 9000 mg arsenic trioxide was rescued by prompt emergency care, forced diuresis, and chelation therapy with 2,3-dimercaptopropanol (BAL) and meso-2,3-dimercaptopropanol (DMSA) (Vantroyen et al., 2004). The clinical doses of arsenic trioxide (5-10 mg i.v.) could induce cardiac injury, such as QT prolongation, arrhythmias, and in extreme cases, cardiac arrest (Evens et al., 2004; Westervelt et al., 2001; Chou et al., 2005). Other adverse effects include skin lesions, gastrointestinal symptoms (Miller et al., 2002; Chou et al., 2005), neuropathy and liver dysfunction are reported with long-term arsenic trioxide use (Miller et al., 2002; Evens, et al., 2004; Chou et al., 2005), and generally tolerable and reversible. In a chronic study in rabbits, arsenic trioxide at a dose of 0.2 mg/kg, i.v. for 30 days produced cardiac injury, with alterations in cardiac function. These adverse effects are reversible after the termination of arsenic trioxide treatment (Wu et al., 2003). Possible secondary cancers have not been reported in patients received arsenic trioxide (Miller et al., 2002; Evens et al., 2004; Chou et al., 2005). However, arsenic-induced cancers may have a long latent period, and the longer time monitoring is needed to verify the carcinogenesis effects of arsenic trioxide or realgar used in traditional remedies.

"The dose makes a poison". In the evaluation of the toxic effects of mineral arsenicals, dose and duration of administration should be critically considered. Although mineral arsenicals in traditional medicines are beneficial and even curative of various diseases, it should be kept in mind that "the right dose differentiates a remedy from a poison". Another important consideration is to balance the benefit and risk. Arsenic trioxide is highly toxic, but to save a life from malignancies, the use of a poison like arsenic trioxide may be justified.

Summary

This minireview discussed mineral arsenicals used in traditional medicines. Orpiment and realgar have quite different chemical features and solubility from arsenolite/arsenic trioxide. The bioavailability of orpiment and realgar are low, but arsenolite/arsenic oxide is high. Pharmacologic data indicate that the use of orpiment and realgar in traditional medicines may be desired in some cases, but the therapeutic basis in most instances remains to be fully justified. Arsenolite/arsenic trioxide has been a major breakthrough as a cure for a subset of human leukemias and its use as a mineral arsenical in traditional medicines prompted this finding. Cardiovascular toxicity is the major concern for arsenic trioxide, and realgar is much less

acutely toxic than arsenic trioxide. Little is known about possible secondary cancers resulting from the long-term use of any of these arsenicals. Similar to the safety evaluation of seafood arsenicals, total arsenic content alone is insufficient for safety evaluation of mineral arsenical-containing traditional medicines, and arsenic speciation, bioavailability, and toxicity/benefit should be all considered in any such evaluation.

Acknowledgements

Abbreviations

As_2S_3, Orpiment; As_4S_4, Realgar; contains arsenic trioxide, As_2O_3, Arsenolite; APL, Acute promyecytic leukemia; PMLRARα, Promyelocytic leukemia-retinoic acid receptor α; MMA, Monomethylarsononous acid; DMA, Dimethylarsinic acid; TMA, Trimethylarsonic acid; As^{5+}, sodium arsenate; As^{3+}, sodium arsenite.

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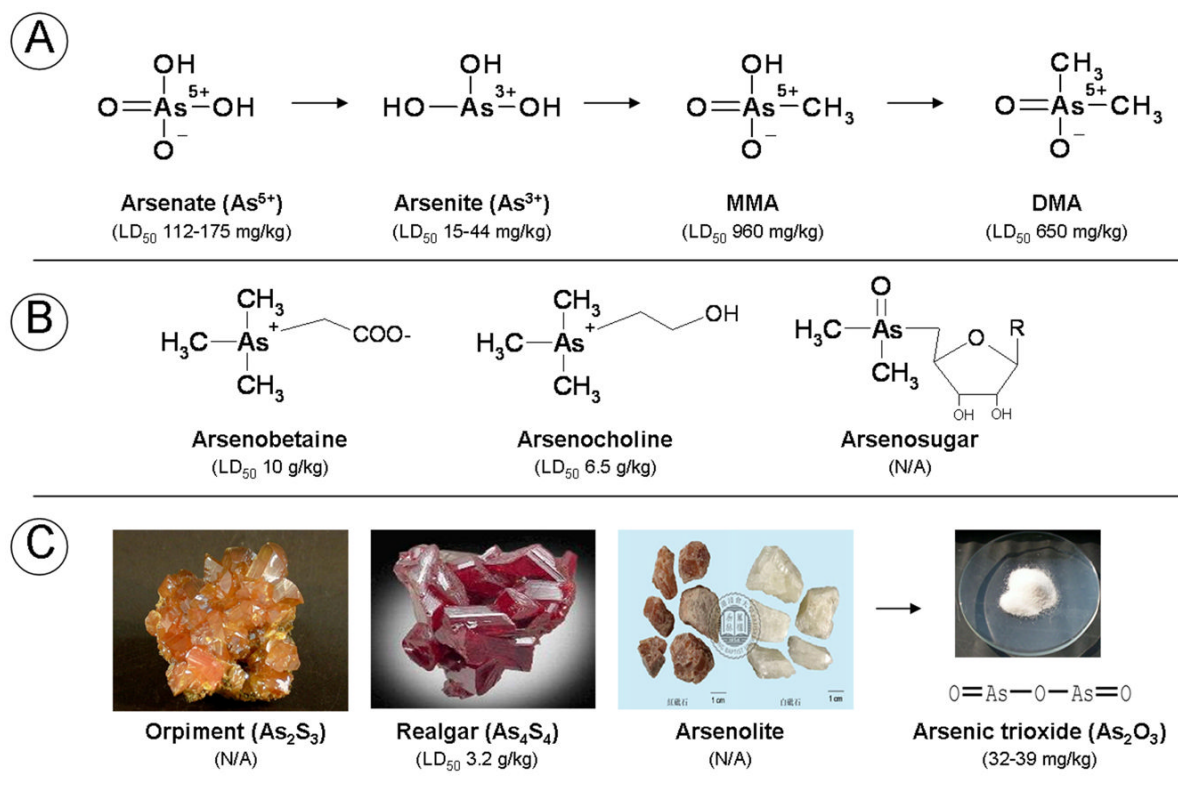**Fig. 1.**
Acute oral toxicity (LD_{50}) of arsenicals in rodents. A: common inorganic arsenicals and their organic arsenical metabolites; B: arsenic species in seafood; C: mineral arsenicals. N/A: LD50 data is not available

Table 1

Natural arsenic-containing minerals in traditional medicines

Name	Popular names	Chemical form	Traditional or historical uses
Orpiment	Yellow arsenic *Arsenikon, Cihuang,*	As_2S_3 arsenic tri sulfide	Cancer, skin diseases, bald head scab disinfectant, antispasmodics, psoriasis
Reaglar	Red arsenic *Xionghuang*	As_4S_4; As_2S_2 arsenic disulfide, arsenic sulfide	Malignancies, skin diseases, sedatives antipyretic, anti-inflammation, unclers
Arsenolite	White arsenic *Pishi*	As_2O_3 arsenic trioxide	Fowlers solution for psoriasis, syphilis Cancer (especially leukemia)

Table 2

Pharmacokinetic studies of orpiment, realgar and arsenolite/arsenic oxide

Arsenicals	Bioavailability	System	Major Findings	Reference
Orpiment	Low	In vitro	Dissolution increase with pH increase	Lantz et al., 1995, Floroiu et al., 2004
	Low GI absorption	Hamster	80% in feces; DMA in urine	Marafente and Vahter, 1987
Reaglar	4%	Human	MMA, DMA in urine	Koch et al., 2007
	Low	Rat	Blood>lung, heart>spleen>liver, kidney	Wang et al., 2003
	Nanoparticles	Cell and rat	Increased bioavailability	Wu and Ho 2006
Arsenic trioxide	High	Rabbit	As^{3+} in blood, DMA in liver and lung	Lin et al., 2005
		Human	60% of iv dose recovery in urine	Fujisawa et al., 2007
		Human	Oral equals to iv bioavailability	Kumana et al., 2002

Table 3

Examples of orpiment, realgar and arsenolite/arsenic trioxide in traditional medicines

Arsenicals	Traditional Medicines	Recipe	Therapeutic effects
Orpiment	Used alone	External use	Scabies, louse-killer, snake biting, skin diseases
	Quingyu Piwen Dan	One of 74 herbs	Detoxication, diarrhea, abdominal pain
Reaglar	*Niuhuang Jiedu Pian*	6.4% realgar in 8 herbs	Antipyretic, common cold, gingivitis, toothache
	Shuzheng Pian	7.1% realgar in 15 herbs	Heatstroke, dizzy, coma, diarrhea
	Hongling San	15% realgar in 7 components	Heatstroke, dizzy, headache, nausea
	Xiao'er Huadu San	11.5% realgar in 7 components	Children detoxication for fester, malignant boil
	Liushen Wan	one of 6 components	Tonsillitis, laryngitis, throat pain, common cold
	Yatong Yili Wan	10% realgar in 4 herbs/ minerals	Toothache, gingivitis, dental caries
	Angong Niuguang Wan	10% realgar in 11 herbs/ minerals	Coma, unconscious, delirium, convulsions
	jujabg Zhwao San	12% realgar in 9 herbs/ minerals	Pever convulsions, delirium, coma
	Shayao	11 % realgar in 11 herbs/ minerals	Heat stroke, coma, abdominal pain
	Xiao'er Qizhen Wan	15% realgar in 19 herbs/ mineral	Children sedatives, antipyretic, laxative
	Jinhuang Baolong Wan	10% realgar in 6 herbs/ minerals	Phlegmesia, asthma, antispasmodics
	Awei Huapi Gao	4% realgar in 24 components	Remove lump and pain, malignancies
Arsenolite	Used alone	External or Internal use	Remove lump, Scrofula, scabies, anti-parasites
	Ailing Yihao	Major component of the mixture	Leukemia and malignancies (Chen et al., 2000)

All the recipe and uses are based on Pharmacopeia of China (2005).

Table 4

Toxicology studies of orpiment, realgar and arsenolite/arsenic trioxide

Arsenicals	Acute Toxicity	Chronic Toxicity	Comments
Orpiment	N/A	Negative in micronucleus assay	High As levels in blood
		Negative in lung tumor formation	
Reaglar	N/A	Cutaneous manifestations	Adverse effects
		Mild GI discomfort in chemotherapy	Tolerable
		Prolonged QT, dose-dependent	Tolerable
		Fatty liver, but no liver fibrosis	Long-term exposure
Arsenic trioxide	Sudden death, poisoning	Cardiac effects and GI effects	Chelation effective
		Skin and GI effects	Tolerable
		No secondary cancer reports	