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Review

The medicinal use of realgar (As_4S_4) and its recent development as an anticancer agent

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ABSTRACT

Ethnopharmacological relevance: Arsenicals have been known as poisons and paradoxically as therapeutic agents. In the early 1970s, Chinese physicians from Harbin revived the medicinal use of arsenicals as anticancer agents. Notable success was observed in the treatment of acute promyelocytic leukemia (APL) with arsenic trioxide (ATO). The FDA approved ATO injection in the year 2000 for the treatment of APL. In contrast, the clinical use of the other arsenical, realgar (As_4S_4), is currently much less established, though it has also long been used in medical history. According to ancient medical records and recent findings in clinical trials, realgar was found as effective as ATO, but with relatively good oral safety profiles even on chronic administration. These give realgar an advantage over ATO in maintenance treatment. Though there is increasing understanding on the mechanisms of action and metabolic profiles of ATO, similar aspects of realgar are unclear to date.
Materials and methods: We outline the use of realgar in traditional medicines, especially in traditional Chinese medicines (TCM) from ancient times to present. The clinical and experimental observations on realgar as a therapeutic agent are described with an emphasis on those findings that may imply the rationale and future directions of realgar as a potential anticancer drug candidate.
Results: There is an increasing understanding in the mechanisms of action of realgar as an antileukemic agent. However, there is still sparse information on its metabolism and toxicity profiles.
Conclusions: Realgar is poorly soluble in water. Recently, several types of realgar nanoparticles (NPs) have been developed. Some of these realgar NPs also possess the unique optical properties of quantum dots. The activities and bioavailability of realgar NPs are much influenced by their sizes, making realgar an interesting biomedical and pharmaceutical research candidate.

Contents

Abbreviations: ATO, arsenic trioxide; APL, acute promyelocytic leukemia; FDA, American food and drug administration; NPs, nanoparticles; CML, chronic myeloid leukemia; TCM, traditional Chinese medicine; A, arsenic sulfide; I, indirubin; T, tanshinone IIA; QDs, quantum dots; PML-RARα, promyelocytic leukemia-retinoic acid receptor-α; AQP9, aquaglyceroporin-9; QTc, corrected QT interval; MMA^V, monomethylarsonic acid; DMA^V, dimethylarsinic acid; MMA^{III}, monomethylarsenous acid; DMA^{III}, dimethylarsinous acid.

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1. Introduction

Arsenic is known to be toxic and carcinogenic and at the same time therapeutically effective for a variety of diseases including cancers. Therefore, comparative assessment of the benefit and risk of arsenic to human health is warranted, particularly when considering its potential medicinal applications. Historically, the medicinal use of arsenic has undergone four development stages: (1) early start at about 100 BC, (2) prosperity through the 19th century, (3) decline in the early 20th century, and (4) revival in recent decades. This trend partially reflects the impacts of balancing benefit and risk of arsenic on its practical applications. Nowadays, it has been well recognized that both benefit and risk of arsenic are strictly dependent on the individual chemical forms of arsenic instead of arsenic content alone (Cohen et al., 2006). More interestingly, studies on the mechanisms of activity for the respective arsenicals suggest that similar mechanisms mediate both their therapeutic activities and their toxicities, in which dose usually has dramatic impacts on their ultimate effects (Miller et al., 2002).

Arsenic trioxide (As_2O_3, ATO) is such a typical and inspiring example showing how a well-known poison can also be used therapeutically as a potent anticancer agent. The first clinical use of ATO to treat certain types of cancers was carried out in China during the 1970s. A group of clinical researchers in Harbin Medical University selected it to treat several types of cancers such as esophageal carcinoma, malignant lymphoma, chronic myeloid leukemia (CML) and acute promyelocytic leukemia (APL) based on the therapeutic principle of traditional Chinese medicine (TCM) of "using a poison to fight against other poisons or malignancy illnesses" (Zhang et al., 1973; Zhang and Rong, 1973). They soon observed some promising responses. Thereafter, more and more clinical trials in China demonstrated that ATO is highly effective and safe in the treatment of APL patients regardless of disease stages (Sun et al., 1992; Zhang et al., 1996). However, ATO was not widely accepted for clinical use in Western medicine mainly because the relevant preclinical testings on its efficacy and safety were still insufficient. Until the mechanisms of the anticancer activity of ATO were better understood, its therapeutic efficacy on APL was gradually recognized globally (Chen et al., 1996; Shen et al., 1997). In 2000, the US Food and Drug Administration (FDA) approved ATO injection, Trisenox™, as a first-line chemotherapeutic agent for newly diagnosed and refractory/relapsed APL patients. Nowadays, ATO is regarded as a promising chemotherapeutic agent for the treatment of APL. Subsequently, it was shown that ATO acts through a variety of mechanisms involving numerous signal transduction pathways. Its cellular effects were mediated through apoptosis induction, growth inhibition, differentiation promotion/inhibition, and angiogenesis inhibition (McCabe et al., 2000; Miller et al., 2002). The multiple actions of ATO suggest that it can potentially offer therapeutic benefits to different types of cancers as a single agent or in combination with other cytostatic or cytotoxic agents. However, the occasional occurrence of sudden death after administration of ATO deters some physicians from using it clinically (Gan et al., 2008).

The success of ATO prompts researchers to explore other arsenic derivatives which could have similar anticancer effects to ATO but fewer adverse effects. Realgar (As_4S_4) was chosen as such a candidate for its good therapeutic reputation and perceived low toxicity in traditional medicines. Here we mainly outline the use of realgar in traditional medicines, especially in TCM from ancient times to present. The clinical and experimental observations on realgar as a therapeutic agent are described with an emphasis on those findings that may imply the rationale and future directions of realgar as a potential anticancer drug candidate.

2. The past and present use of realgar in traditional medicines

Pure realgar is an orange-red crystalline mineral (α-phase). The spatial structure of realgar is analogous to that of sulfur (S_8), in which 4 arsenic atoms regularly replace 4 of the 8 sulfur atoms to form a similar ring, but the monoclinic crystal structure of realgar is different from the orthorhombic symmetry of sulfur. Realgar is soft and sectile; and usually occurs in granular, compact, or powder form, as described by its name in the Arabic words for "powder of the mine". Realgar ore most commonly occurs in hydrothermal veins, and is also often found as hot spring deposits and volcanic sublimations. Notable realgar mines are found in HuNan in China, Switzerland, Japan, Macedonia, Utah in USA, and Romania, etc.

Processing of realgar ore requires the removal of the associated minerals including orpiment, calcite, stibnite and other metal sulfide ores. Realgar is poorly soluble in aqueous and most organic solvents due to its high intrinsic lattice energy. Therefore, it needs to be powdered before use. Traditionally, realgar was mainly used as a pigment and in internal medicines. Other former applications include manufacturing shot, depilating and tanning hides, pyrotechnics, and controlling pests. The following two sub-sections describe the historical and modern medicinal use of realgar in China and other countries.

2.1. Use of realgar in Ancient Chinese Medicine

In China, realgar, also called *Xiong Huang* (雄黄), has been traditionally used for many centuries. The first medicinal use of realgar in China was historically recorded in *Shen Nong Ben Cao Jing* (神农本草经), the first Chinese Materia Medica before 100 BC, in which realgar-containing pastes were used in the treatment of certain skin problems like carbuncle. An elixir made from realgar together with other materials was once claimed to have the power of immortalizing humans, according to the record in the book of *Huai Nan Tzu* (淮南子 , 179 - 122 BC). In Ancient China, realgar was thought to possess magical power to fling off demons and venomous snakes. Nowadays, the custom of drinking realgar wine during the Dragon Boat festival for the belief of warding off diseases and driving away evil spirits is still common among the inhabitants in areas around Yangtze River.