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# Arsenic prepared by Chinese alchemist-pharmacists

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Dear Editor,

The discovery of artemisinin is just one of the gifts from traditional Chinese medicine to the world. Clinical studies have shown that arsenic trioxide, an ancient drug used in Chinese medicine, is an effective and relatively safe treatment for acute promyelocytic leukemia (APL). In particular, Chinese alchemy has attracted attention as it gave rise to a wealth of innovations in the medical and chemical field, although the alchemists' enterprise was not chemistry. From the late 1960s to the 1980s, significant experimental investigations suggested that Chinese alchemist-pharmacists prepared arsenic (As) even before the Western alchemist Albertus Magnus (1193–1280) did. Albertus Magnus is widely recognized as the first one to have prepared arsenic by heating orpiment with soap (Zhu and Ren, 2008). However, current literature provides evidence favoring its preparations by Chinese alchemist-pharmacists. Indeed, early in the 3rd century BC, Chinese alchemist-pharmacists widely preferred arsenic minerals, such as orpiment and realgar, to prepare elixirs because of the special colors and stability of the minerals.

Based on a reproduced experiment of Sivin (Sivin, 1968), it was proposed that the Chinese alchemist-pharmacist Sun Simiao (581–682) had prepared arsenic long before the Westerners did. Since then, this proposition has engendered interest as well as further research. Subsequent studies have argued that the first person to obtain arsenic is not Sun but another alchemist-pharmacist named Ge Hong (283–363) (Zheng and Yuan, 1982; Zhao and Zhang, 1985). Zhao and Zhang reported that the formula of Ge could be understood through the process by which he obtained the element. The authors later reconsidered the results of their experiments and argued that Ge may have obtained arsenic even before Albertus Magnus did (Zhao and Zhou, 1998). Because the two formulas of Ge and Sun can be understood in other ways, especially the vague descriptions of the ratio of the materials and the range of the heating temperature, the previous experiments raised the following questions. Did Ge obtain the substance called elemental arsenic in modern chemistry? Can arsenic be prepared following Sun's formula? Are there other records in Chinese history that suggest the preparation of arsenic? What did Chinese alchemist-pharmacists use arsenic for? How can we use the reproduced experiments as a reasonable approach to explore alchemy and traditional medicine?

To address these issues, we reconstructed the experiments under the directions of the two formulas of Ge and Sun. We further consulted *Dao Zang* (The Taoist Canon), which collected numerous Chinese alchemical scriptures. From this Canon, we found more alchemical formulas, through which we were able to reproduce the important ones. The exact time when arsenic was prepared and how Chinese alchemist-pharmacists recognized it are also discussed in the present paper.

We conducted the first group of experiments according to the process described by Ge. He regarded realgar treated with some materials as a type of elixir and reported that one of his products was cloth-thin and icewhite (Figure S1A in

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Supporting Information). However, his description of the way he obtained realgar was very ambiguous, such that it can be interpreted in three ways: realgar was heated with saltpeter or with the large intestines of a pig or rosin; realgar was heated with the latter three materials in sequence; or the four materials were heated simultaneously. The work of Zheng and Yuan showed that arsenic with a silvery white color could be obtained according to the first two processes. However, they proposed that alchemist-pharmacists should not make use of the third process because the mixture of the four materials heated can lead to an explosion. Subsequently, Zhao and Zhang proposed the possibility of heating the mixture without explosion; however, the exact conditions were unclear. Following the third process, we conducted the controlled experiments in different conditions with varying ratios of the materials and heating temperatures. The exact experimental conditions we chose were determined according to whether we could obtain the product Ge described as being "as white as ice". We found that the reaction was performed safely through the following parameters: realgar∶saltpeter $\leqslant$2.5∶1 in weight and temperatures between 250°C and 300°C. In addition, arsenic was obtained in the reaction with intestines plus pine resin: saltpeter $\geqslant$2∶1 in weight. Although $As_2O_3$ could be obtained individually without arsenic during our experiments, it was mixed with the sublimate realgar. This combination produced a milk yellow color, which does not match Ge's description as being "white as ice". Therefore, it is indeed factual that Ge observed and prepared the substance that we call arsenic in modern chemistry.

We conducted the second group of experiments according to the process described by Sun. Sun claimed that he made an elixir called "scarlet-snow-and-flowing-pearl". Through a two-step process, he sequentially heated realgar with vinegar and common salt, followed by cooked rice (Figure S1B in Supporting Information). In this experiment, we gradually increased the heating temperature according to the directions in the formula, in which a low fire was applied first, followed by a roaring fire, and finally, the lower part of the combustion chamber was maintained to have the same color as the fire. In our reproduced experiment, the reaction vessel was made of two crucibles placed mouth to mouth and sealed. The crucibles we used were made of porcelain rather than nickel, considering Sun's vessel was iron and wrapped completely with the clay. Although the vessel was used correctly in the study of Zhao and Zhang, the condition of their products was not consistent with that described by Sun. We found that arsenic was not obtained after the first heating; however, after the second heating with a temperature higher than 500°C, it was sublimated to

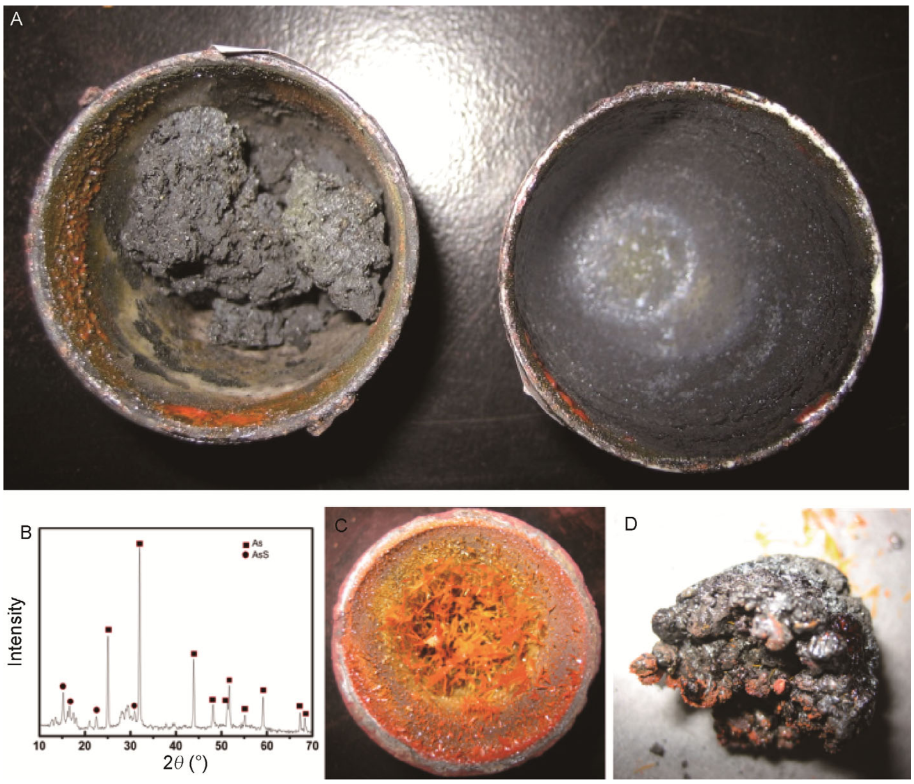


**Figure 1** A, Photograph of the products in the reproduced experiment to create the "scarlet-snow-and-flowing-pearl" elixir when the highest reaction temperature was elevated to 550°C. B–D, Results of the experiment reproducing "scarlet-snow-and-flowing-pearl" elixir when the highest reaction temperature was elevated to 450°C. B, X-ray powder diffraction (XRD) pattern of the products in the lower crucible. C, Photograph of the upper crucible with the products. D, Photograph of the products removed from the lower crucible.

the upper crucible, thus overlapping the sublimate realgar (Figure 1A). The alchemist-pharmacists could not have observed the products as having a "scarlet silken thread" appearance or having the shape of a "pendant string of pearls" as described in the formula. Moreover, the color of the lute glow was the same carmine color as described in the formula when heated at a temperature higher than 400°C. According to description made by Sun regarding the color of the heated vessel and the product, we reproduced the reaction below 500°C and observed arsenic, which was reduced by cooked rice in the lower crucible (Figure 1B). However, the needle crystal of realgar, which was like "scarlet-snow" in the upper crucible (Figure 1C), was so conspicuous that the silvery white arsenic in the lower crucible (Figure 1D) was ignored by the alchemist-pharmacists. We conclude that the highest temperature at which the alchemist-pharmacists performed the process was between 400°C and 500°C, and arsenic was obtained in the lower crucible. Furthermore, Sun gave a formula that read: "to tame realgar and orpiment by tin," which denoted that one of the products he produced was arsenic (Zhao and Zhang, 1985). However, he was only attracted by the golden tin bisulfide ($SnS_2$) and ignored the arsenic.

In addition, we conducted the three other formulas in *Dao Zang*. The products were identified by XRD and X-ray photoelectron spectroscopy; however, arsenic was not a component of the product.

Based on the earlier works and our experiments, we determined the possibility of obtaining arsenic from the formulas recorded in *Dao Zang*. Chinese alchemist-pharmacists developed many processes to "tame Pi" in some scriptures completed after Sun (Figure S1C in Supporting Information), especially during the 12th–13th century. Here, the "Pi" was $As_2O_3$, "to tame" indicates the deactivation or prevention of a substance's sublimation, and "to tame Pi" was equivalent to making arsenic trioxide ($As_2O_3$) un-sublimate by treating it with carbon-rich materials, such as herbal medicine, honey, or petroleum. At 150°C–200°C the said materials can be changed to charcoal, which can reduce As (III) to As (0). Relatively pure Arsenic was obtained according to the two formulas, and the properties of the reduced arsenic, such as having a silvery white color and a very hard composition, were consistent with the description of the alchemist-pharmacists. Furthermore, we found 19 other formulas (Table S1 in Supporting Information) "to tame Pi," that were completed during this period and collected in *Dao Zang*, according to which arsenic can be obtained. During that time, arsenic was not only widely prepared but also remarkably pure because of the special apparatus and materials used. Alchemist-pharmacists used an earthenware crucible or kettle covered with a piece of tile or bowl to which water was continuously added for cooling to collect the sublimed products. Clearly, a larger amount of pure arsenic could be prepared in the apparatus with the cooling effect of water. The descriptions in the formulas made it clear that alchemist-pharmacists observed the "tamed Pi"-like snow mountain adhering to the bottom of the tile or bowl. They also emphasized that the bright silver product could only be found at the bottom of the tile or bowl. The effect of the glutinous materials was important for alchemist-pharmacists to obtain purer arsenic. Four formulas applied flour, honey, wax, and petroleum to be mixed and wrapped sufficiently with the arsenic minerals. A high yield of arsenic was obtained with the said formulas because the reaction was performed completely. More importantly, arsenic trioxide ($As_2O_3$) was fixed with the glutinous materials so as not to sublimate and mix with the reduced arsenic. Two formulas even directly used charcoal as the material, which is the currently used method for the industrial preparation of arsenic. The arsenic prepared during those periods was mostly applied as a "projection" to transmute or intenerate common metal to medical gold or silver. In fact, those medical gold or silver are alloys of Cu-As or Cu-As-Sn with golden or white color and were considered to be superior to the natural gold or silver by alchemists.

The results of the reproduced experiments and documentation confirm that Chinese alchemist-pharmacists were the first to prepare arsenic before the Westerners. Ge prepared arsenic in the early part of the 4th century. Relatively pure arsenic was obtained, and its physical properties were recognized only in the 12th–13th century when it was widely used to make alloys. We do not intend to preoccupy the present historical conversation with ancient anticipations of modern chemistry nor do we see alchemy as a fledgling science. In fact, Chinese alchemist-pharmacists did not derive the conceptions of individual elements; those were the result of the Western scientists. However, recognition was not given to the early Chinese alchemist-pharmacists. Nevertheless, given that arsenic and its compounds were widely used as a drug in classical Chinese medicine, the present discussion can guide us toward a better understanding of the relationship between Chinese alchemy and medical treatment.

**Compliance and ethics** *The author(s) declare that they have no conflict of interest.*

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## SUPPORTING INFORMATION

**Figure S1** Formulas for taking realgar and making the "scarlet-snow-and-flowing-pearl" elixir, and Immortal Ge seeing precious arsenic.

**Table S1** Other formulas used for preparing arsenic

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