Detection of High Levels of Arsenic and Mercury in Some Chinese Traditional Medicines Using X-Ray Fluorescence Spectrometry

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We examined the mineral contents in Chinese traditional medicines from Japanese or Chinese markets by X-ray fluorescence spectrometry, and found extremely high levels of arsenic (N.D.–11.8%) and/or mercury (N.D.–18.8%) in medicines from Chinese markets but not Japanese markets. Such traditional medicines also contained sulfur in high levels, suggesting that these toxic metals present as their respective sulfide. Arsenic was partially eluted with hot water, artificial gastric juice, or artificial intestinal juice from *rokushingan* (Liushenwan), one of the most famous Chinese medicines. These results suggest that high arsenic-Chinese medicines are harmful to human beings and special attention should be given to traditional medicines in Chinese markets.

Key words —— arsenic, mercury, toxic element, Chinese traditional medicine, X-ray fluorescence spectrometry

INTRODUCTION

Chinese traditional medicines are familiar to many people and available in both Japanese and Chinese markets. These medicines consist of some crude drugs, which are natural products that usually contain various metals. The inorganic components are expected to be responsible for the pharmacological effects.[1,2] On the other hand, high levels of harmful metals might have toxic effects. Although metals in crude drugs have been examined,[1–8] there is little information available on Chinese traditional medicines. Therefore, we examined the presence of metals in Chinese traditional medicines by X-ray fluorescence spectrometry. As a result, high arsenic and mercury contents were detected in some traditional medicines from Chinese markets.

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MATERIALS AND METHODS

Materials —— Chinese traditional medicines were purchased from Chinese and Japanese markets (Table 1).

X-Ray Fluorescence Analysis —— The Chinese traditional medicine samples were powdered with an agate mortar and pestle, and then kept in a silica gel desiccator for more than 24 hr. Fifty mg of each powdered sample was mixed with 100 mg of cellulose powder with an agate mortar and pestle. Next, 150 mg of each mixture was pressed into a 2.0 cm-diameter pellet at 10 tons of pressure. X-ray measurements were performed on the pellet samples with a wavelength-dispersive X-ray fluorescence spectrometer (Rigaku RIX3100), consisting of a chromium or rhodium anode X-ray tube. Element contents were analyzed using the fundamental parameter (FP) method.[9]

Analysis of Arsenic and Mercury Eluted from a Rokushingan (Liushenwan) Sample with Various Solutions —— Sample powder (15 mg) of *rokushingan* was stirred at 37°C for 30 min in artificial gastric or artificial intestinal juice (20 ml).[10] In the case of water, after the sample was stirred in boiled water (20 ml) for 10 min, the solution was cooled to 37°C. Each solution was filtered by a membrane filter (0.45 μm) and then freeze-dried. The weights of the resulting powders were adjusted to 150 mg by the addition of cellulose powder. X-ray

Table 1. Chinese Traditional Medicines at Chinese and Japanese Markets

Sample No.:	Name	Market
Chinese Market		
1:	Qianjinsan	Harbin City
2:	Niuhuangqingfeisan	Tonghua City
3:	Feiersan	Heilong Jiang Province
4:	Baochiwanyingsan	Tianjin City
5:	Tiewadan	Harbin City
6:	Yingerle	Harbin City
7:	Yingerbaofeining	Harbin City
8:	Jierezhenluesan	Harbin City
9:	Xiaoerqifengsan	Harbin City
10:	Elerle	Qiqihar City
11:	Yingersu	Harbin City
12:	Wawabao	Nanyangzhiyaochang
13:	Feierwanyaopian	Zhengzhou City
14:	Xiaoerqiyingwan	Harbin City
15:	Duzhonghuguwan	Guiyang City
16:	Liushenwan	Jiangsu Province
17:	Liushenwan	Shanghai City
18:	Liushenwan	Shanghai City
19:	Liushenwan	Jiangsu Province
20:	Liushenwan	Shanghai City
21:	Houyanwan, Laryngitis pills	Chengdu City
22:	Zhibaosanbianwan	Shandong Province
23:	Renshenzaizaowan	Harbin City
24:	Jufangniuhuangqingxinwan	Shanxi Province
25:	Teidiwan	Beijing City
26:	Shihuyeguangwan	Beijing City
27:	Lurongpuwan	Tianjin City
28:	Luxinpian	Sichuan Province
29:	Lurongfen	Sichuan Province
30:	Anticancerlin	Shanghai City
31:	Yunnanpaiyao	Yunnan Province
32:	dingkundan	Shanxi Province
33:	Wuchasengcha	Yichun City
34:	Puerhfangcha	Yunnan Province
Japanese Market		
35:	Kyushin	Kyushin Pharmaceutical Co.
36:	Rokushingan	Ohki Pharmaceutical Co.
37:	Mamushihorumo (gold pills)	Sakamoto Kanpo Pharmaceutical Co.
38:	Mamushihorumo (capsules)	Sakamoto Kanpo Pharmaceutical Co.
39:	Ottovin (gold pills)	Nihon Iyakuhin Seizou Co.
40:	Seikeikannogan	Showa Kagaku Kougyou Co.
44:	Rokushingan	Kameda RisaburoYakuho Co.
45:	Chuseirokushingan	Matsuura Yakugyou Co.
Japanese Market (Made in China)		
41:	Soukasanrokugan	Iskra Industry Co. (Tianjin Lexintang)
42:	Nissuiseisingan	Nissui Pharmaceutical Co. (Beijin Tongxintang)
43:	Shihousanbengan	Iskra Industry Co. (Yantaizhongyazhiyaochang)

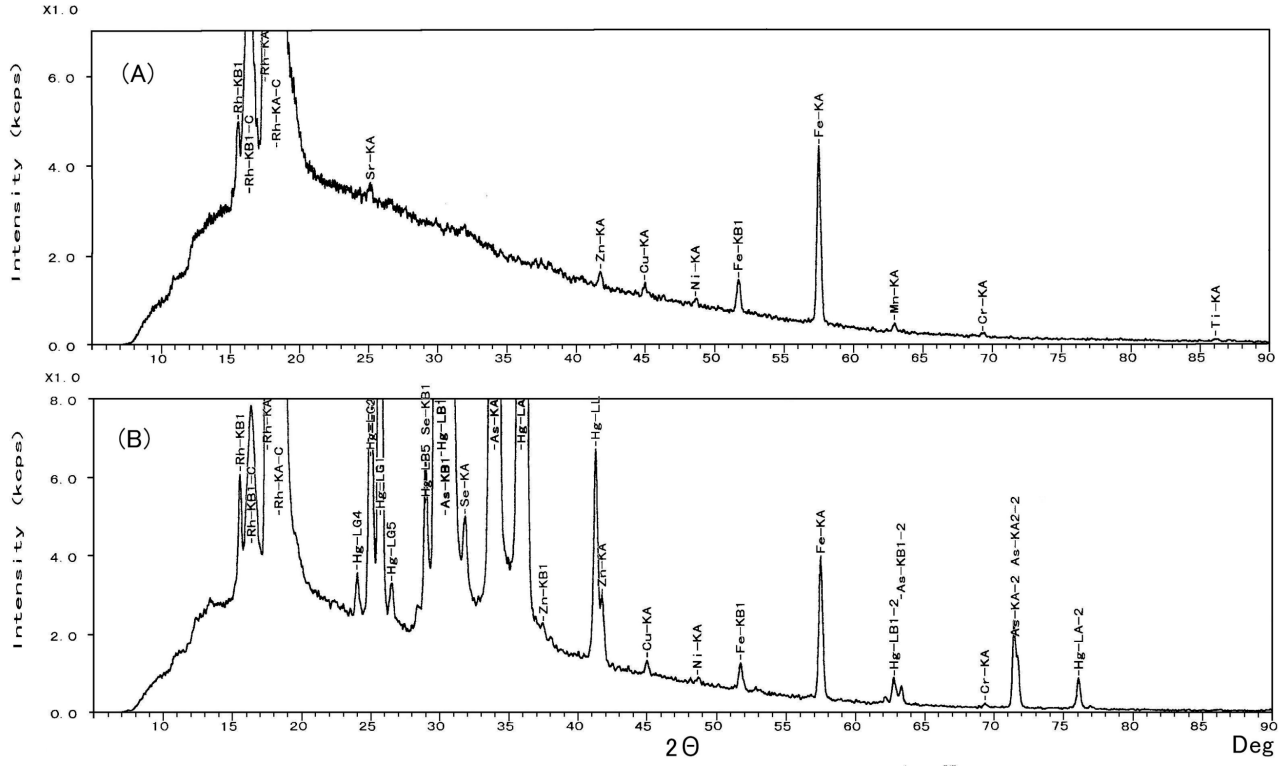

Fig. 1. X-Ray Fluorescence Spectra of Two Samples of Chinese Traditional Medicines

(A), a normal Chinese traditional medicine, Wawabao. (B), a typical Chinese traditional medicine, *rokushingan* (Liushenwan) containing high levels of arsenic and mercury.

fluorescence spectrometric measurement was performed on the pellet samples as described above.

RESULTS AND DISCUSSION

Figure 1 shows the X-ray fluorescence spectra for a normal Chinese traditional medicine, Wawabao (A) and a typical Chinese traditional medicine, *rokushingan* (Liushenwan) (B), which contained high levels of arsenic and mercury. Qualitative analysis was easily performed based on the peak position (diffraction angle, 2θ) of the characteristic X-rays generated from the sample materials. The characteristic X-rays (Kα and Kβ for arsenic; Lα, Lβ and Lγ for mercury) of arsenic and mercury appeared at specific positions in the lower spectrum (B, *rokushingan*) with extremely strong intensity, compared with the results in the normal sample with undetectable low levels (A, Wawabao). High arsenic and mercury contents were also detected in almost all of the other *rokushingan* samples and in some other kinds of Chinese traditional medicines.

Quantitative analysis requires correction for the preliminary and secondary effects of the sample matrix. The X-ray fluorescence technique should be suitable for nearly all elements heavier than sodium. Since the matrix effects could be calculated by assuming that the residual composition is cellulose, quantitative analysis using the FP method is possible.

Table 2 shows the recovery rates of arsenic and mercury added to normal Chinese traditional medicine (Wawabao). Recovery rates for 1, 3, and 10%(w/w) were between 90–110%. Thus, this method appears to be suitable for the determination of arsenic and mercury in these Chinese traditional medicines.

Table 3 shows the analytical results for several kinds of Chinese traditional medicines by X-ray fluorescence spectrometry. Photographs of the Chinese traditional medicines that contained arsenic and/or mercury at high levels are shown in Fig. 2. A high mercury concentration (1.2–18%) was detected in 14 of the 34 samples (purchased in China), and a high arsenic concentration (0.6–11%) was detected

Table 2. Recovery Rates of Arsenic and Mercury from Traditional Medicine (Wawabao)

Added[a)]	Arsenic		Mercury	
	Recovery (%)[b)]	C.V. (%)	Recovery (%)[b)]	C.V. (%)
10	95.3	3.0	94.3	4.4
3	104.5	4.5	108.3	2.8
1	97.4	4.1	103.4	3.9

C.V., coefficient of variation. *a*) Amount is expressed as %(w/w) of the medicine. *b*) Values are means ($n = 5$).

Table 3. Chinese Traditional Medicines Containing Arsenic and Mercury at High Levels

Arsenic Content (%)	Mercury Content (%)	Sample No.	Name	Description[a)]
11.5	—	20	Liushenwan	no
9.2	—	13	Feierwanyaopian	no
9.0	7.2	17	Liushenwan	no
8.8	6.9	18	Liushenwan	no
8.6	6.0	19	Liushenwan	no
8.3	6.3	16	Liushenwan	no
5.0	3.0	14	Xiaoerqiyingwan	Cinnabaris
2.1	1.2	2	Niuhuangqingfei-san	Cinnabaris Realgar
0.6	1.2	24	Jufangniuhuang-qingxinwan	Cinnabaris Realgar
—	18.8	9	Xiaoerqifengsan	Cinnabaris
—	16.3	5	Tiewadan	Cinnabaris
—	12.6	4	Baochiwanying-san	Cinnabaris
—	7.7	1	Qianjinsan	Cinnabaris
—	2.4	7	Yingerbaofeining	Cinnabaris
—	1.8	8	Jierezhenluesan	Cinnabaris
—	1.5	6	Yingerle	Cinnabaris

a) Mineral crude drugs (Cinnabaris, Realgar, or Orpimentum) noted as ingredients. —: not detected.

in 9 samples. An arsenic concentration of about 11% was detected in 1 of 5 samples of *rokushingan* tested, and both 6–7% mercury and 8–9% arsenic were detected in the remaining 4 samples. On the other hand, high levels of arsenic and mercury were not detected in 11 samples in Japanese markets (including medicines imported from China). These results suggest that some Chinese traditional medicines purchased in China contain high levels of arsenic and/or mercury.

In considering the toxicity of these two elements, their chemical forms in the medicines are important. X-ray florescence spectrometry can also clarify the contents of some non-metallic elements. A tendency for a greater sulfur content was observed among arsenic and/or mercury-containing medicines. Figure 3 shows the relationship between the analytical values for the sulfur content and the calculated values for sulfur content assuming that the two toxic metals are present as their respective sulfides. An apparent correlation was observed between the analytical values and the calculated values, especially in all *rokushingan* samples, suggesting that arsenic and mercury exist as their respective sulfides in these medicines. In practice, Cinnabaris (HgS), Orpimentum (As_2S_3) or Realgar (AsS) sometimes used for the preparation of traditional medicines. The high contents of both arsenic and mercury found in the medicines probably arise from such mineral crude drugs.

In general, these mineral crude drugs are thought to be insoluble. HgS actually has very low solubility (solubility constant: 3×10^{-54})[11] but AsS and As_2S_3 are not completely stable.[12] Thus, the elution behavior of these two metals from the medicines was examined. Table 4 shows the soluble amount of these elements with water, artificial gastric or artificial intestinal juice from a *rokushingan* sample. Although

Fig. 2. Chinese Traditional Medicines Containing High Levels of Arsenic and/or Mercury

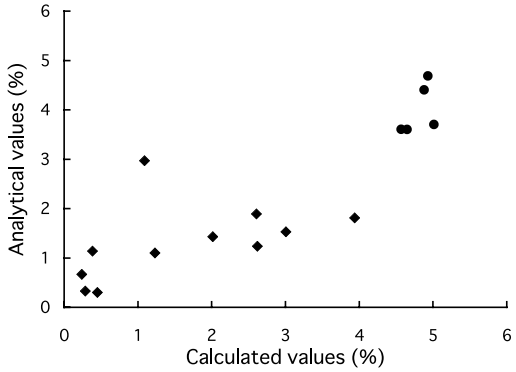

Fig. 3. Relationship between Analytical Values of Sulfur Content and Values Calculated from the Arsenic and Mercury Contents[a)]
a) The values were calculated assuming that arsenic and mercury exist in the medicines as their sulfides. ●: *Rokushingan* samples, ◆: Others.

Table 4. Elution of Arsenic from a Chinese Traditional Medicine, *Rokushingan* (Liushenwan)

	Amount of eluted arsenic in 15 mg of Liushenwan	Concentration of eluted arsenic in Liushenwan
Rokushingan (Liushenwan)	1.25 mg[a)]	8.3%[a)]
Hot water	9.75 μg	650 ppm
Artificial gastric juice (pH 1.2)[9)]	6.0 μg	400 ppm
Artificial intestinal juice (pH 6.8)[9)]	14.3 μg	950 ppm

a) Arsenic content of original *rokushingan*.

mercury could not be detected in any solutions by X-ray fluorescence spectrometry (data not shown), in all cases arsenic was obviously eluted from the *rokushingan* sample to some extent (~1%) for 30 min. The symptoms of acute arsenic poisoning in human by the oral route (nausea, vomiting, diarrhea, burning of the mouth and throat, and severe abdominal pains) have frequently been described. Chronic exposure to smaller toxic doses results in weakness, prostation, and muscular aching with few gastrointestinal symptoms. Skin and mucosal changes usually develop, together with a peripheral neuropathy and linear pigmentation in the fingernails. Headache, drowsiness, confusion, and convulsions are seen in both acute and chronic arsenic intoxication. Excess arsenic uptake [provisional tolerable weekly intake (PTWI): 15 μg/kg body weight/week] may cause poor health. In this study, the estimated weekly intake of arsenic from these Chinese medicines was calculated to be very high and not safe for humans. For example, 750 μg of arsenic (PTWI/50 kg) corresponds to only 9.0 mg of *rokushingan* (arsenic: 8.3%), whereas the usual weekly dosage is about 630 mg [8–9 pills (about 30 mg) each time, three times daily]. In the case of *rokushingan*, since 630 mg is administered per week, even if even the bioavailability is only near 1%, the estimated 520 μg of arsenic is comparable to 750 μg of arsenic (PTWI/50 kg). Another problem is the fact that children's medicines frequently contain arsenic and mercury at high levels (Fig. 2 and Table 3). For example, Feierwanyaopian, Xiaoerqiyingwan, and Xiaoerqifengsan contain 9.2% arsenic, 5.0% arsenic and 3.0% mercury, and 18.8% mercury, respectively. Furthermore, although the traditional medicine contains mineral drugs of arsenic or mercury, these are not often shown as principal ingredients (Table 3). Therefore, people might take arsenic and mercury at high levels without knowing it. The Chinese traditional medicines obtained from Japanese markets did not contain these toxic metals at high levels because of the prohibition on the medicinal use of arsenic- and mercury-containing substances in Japan [In Japan, drugs that contain more than 10 ppm arsenic (as As_2O_3) are not permitted for use as medicines.].[13)] However, it is now possible to purchase such toxic metal-containing medicines unknowingly on the Internet or while traveling in foreign countries.

In conclusion, some Chinese traditional medicines in Chinese markets contain extremely high levels of arsenic and/or mercury, sometimes with-

out being described as principal ingredients. Especially, arsenic may be harmful because of its partial solubility. Special attention should be paid to such traditional medicines in Chinese markets.

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