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Rapid screening and quantification of heavy metals in traditional Chinese herbal medicines using monochromatic excitation energy dispersive X-ray fluorescence spectrometry†

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Traditional Chinese herbal medicines are subject to heavy metal contamination. Standard detection methods are too complicated, time-consuming, and expensive for routine analysis, so low-cost methods are in high demand for rapid on-site screening. This study reports a high-sensitivity X-ray fluorescence (HS-XRF) method to determine As, Pb, and Cd residues simultaneously in herbal medicines. It couples monochromatic excitation energy dispersive X-ray fluorescence spectrometry and the fast fundamental parameters method. Each test takes only 10–30 min and costs 1/10th to 1/5th of the standard method. The detection limits, precision and accuracy were evaluated using different approaches, and application notes in practice are also proposed. This study is the first attempt to establish and evaluate HS-XRF in analyzing multiple heavy metals in herbal medicines. This rapid screening method would promote the testing efficiency and thus improve the monitoring of heavy metal contamination in herbal medicines.

Introduction

Traditional Chinese herbal medicines and derived bioactive compounds have been used not only in East Asia, but also in Western cultures with government licenses, such as artemisinin that was adopted in the WHO's standard treatment for malaria.[1] A main concern of the traditional Chinese herbal medicines is the potential heavy metal contamination in the raw materials or inadequately processed products.[2] Heavy metal toxicity may lead to severe chronic and acute symptoms; so regulatory authorities pay continuous attention to monitoring heavy metal residues in herbal drugs and food supplements.[3,4]

Inductively coupled plasma-mass spectrometry (ICP-MS) is currently the gold standard method to determine heavy metal residues,[5] supplemented by atomic absorption spectrometry (AAS).[6] However, the corresponding pretreatment and digestion of samples are complex, time-consuming, and dangerous, which also causes contamination and inaccurate recovery. In addition, the average cost per test is high due to expensive critical equipment, consumables, and the requirement of certified laboratories.[7,8] X-ray fluorescence spectrometry (XRF) is a rapid and simple technique that has been used in many fields for various commercialized applications, such as environmental monitoring, quality control of cosmetics, and food analysis.[9–11] XRF-based methods require no or minimum sample preparation, which is exceptionally suitable for rapid screening of herbal medicines that are mainly dried plant pieces and slices. Compared with ICP-MS, XRF-based methods eliminate the troublesome HNO_3 digestion, shorten the overall turnaround time from hours to 10–30 min, as well as reduce the economic cost, safety risk, and environmental impact. Not surprisingly, XRF-based methods have been adopted in the latest edition (2020) of the Chinese Pharmacopoeia for element analysis in traditional Chinese herbal medicines.[12]

Nevertheless, the application of XRF-based methods in detecting heavy metal residues in herbal medicines is still in its infancy possibly due to challenges from two aspects. On the instrumentation side, the performance (*e.g.*, sensitivity, accuracy) of conventional XRF spectrometers suffers from a strong matrix effect in testing complex samples, especially for energy dispersive type systems. More preferred than wavelength

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dispersive systems, the energy dispersive X-ray fluorescence (ED-XRF) technique is ideally suitable for analyzing various and truly unknown samples in a high-throughput manner.[13] This advantage is precisely demanded by regulatory agencies in rapid screening of a large number of various herbal medicine samples. In the past two decades, significant improvement has been achieved in manufacturing critical parts and optimizing system design for ED-XRF instruments. On the data analysis side, the challenge in establishing reference database(s) could be the most limiting factor, especially for quantitative analysis of multiple elements. Quantitative XRF usually relies on various calculation methods *via* empirical or theoretical approaches. Empirical approaches, typically empirical influence coefficients, require multiple analytical standards of each species, which are very unlikely available for hundreds of traditional Chinese herbal medicines. Theoretical approaches calibrate fluorescence *via* iteration based on the theoretical relationship between the measured X-ray intensities and the concentrations of elements in the sample.[14] Classical fundamental parameters and many further developed approaches and strategies (*e.g.*, matrix correction, compensation, Monte Carlo) are available depending on specific application scenarios.[15] To date, there is only one study reporting the detection of cadmium in five herbal medicines using an ED-XRF spectrometer.[16]

In the current study, we reported the use of monochromatic excitation energy dispersive X-ray fluorescence spectrometry coupled with the fast fundamental parameters (fast FP) method to achieve rapid quantification of arsenic (As), lead (Pb), and cadmium (Cd) in traditional Chinese herbal medicines. In the developed instrument, monochromatic excitation is achieved with a doubly curved crystal that filters and focuses the source X-ray three-dimensionally,[17,18] thus reducing the scattering background and improving the detection limit. Meanwhile, the fast FP method enables rapid calculation of X-ray spectra (within a second for each sample), enabled by coupling an advanced mathematical model with the initial database of fundamental parameters.[19] The satisfactory performance of the current high-sensitivity X-ray fluorescence (HS-XRF) method was verified by ICP-MS, meeting the demand for rapid screening and quantitation of Cd, As, and Pb in traditional Chinese herbal medicines and complying with the regulatory requirements. To the best of our knowledge, this is the first study to establish and evaluate HS-XRF for analyzing multiple heavy metals in sample matrices of herbal medicines.

Experimental

Sample preparation

The *Panax notoginseng* (powder) quality control sample was obtained from LGC Group (UK). Cellulose (powder) and other reagents were at least analytical grade. Herbal medicine samples (99 samples, 37 species) were collected from local pharmacies and provided by Tianjin Customs. The dried medicine samples were ground using a laboratory grinding mill and then passed through a 60-mesh sieve. The sample powder (<250 μm) was divided for further preparation for HS-XRF and ICP-MS. For HS-XRF, 3 g of sample powder was transferred into a mold and then coated with boric acid. Then, 20 MPa pressure was applied for 60 s using a pellet press (Keqi High & New Tech Co., Ltd, Tianjin), forming a sample pellet (diameter = 30 mm, thickness = 5 mm). For ICP-MS, 0.4 g of sample powder was mixed with 6 mL of nitric acid at 130 °C for 30 minutes. Then, the mixture was digested using a microwave digestion system (Multiwave PRO, Anton Paar, VA, US) with the following temperature profile: ambient to 120 °C over 10 min; 120 °C for 2 min; 120 °C to 190 °C over 4 min; 190 °C for 20 min. After digestion, the solution was evaporated to near dryness, cooled down to room temperature, and then diluted with fresh ultrapure water (Milli-Q, Millipore, USA) to 50 mL.

Instruments and parameters

A portable high-sensitivity XRF heavy metal analyzer was developed for XRF measurement and analysis (PHECDA-PRO). The core parts include a side window X-ray source with a tungsten target (max. power = 12 W; max. excitation voltage = 70 kV; max. current = 400 μA), a full focus doubly curved crystal to generate a monochromatic excitation spot (oval, area = 84.4 mm^2, $2a$ = 11.2 mm, $2b$ = 9.6 mm), and a silicon drift detector (Mn : Kα: 135 eV; max. counting rate = 800 kcps @ −10) (Fig. 1). The doubly curved LiF crystal monochromatizes and focuses high intensity, characteristic X-rays emitted by the microfocus spot X-ray tube to a focal plane of tens to hundreds of micrometers in diameter *via* Bragg diffraction. Thus background noise from the Bremsstrahlung radiation is eliminated and a much higher peak-to-background ratio is achieved for improved quantitative analysis. The saturation thickness of the sample is 5 mm approximately. The tube voltage is 30 kV (As, Pb) or 70 kV (Cd), and the measurement time is 200 s with a dead time of 30% (As, Pb) or 40%(Cd). The quantitative analysis software based on fast FP is integrated, which achieves rapid analysis *via* fast iteration to minimize the difference between the predicted and measured fluorescence signals until satisfactory.[20] An Agilent 8800 ICP-MS/MS system

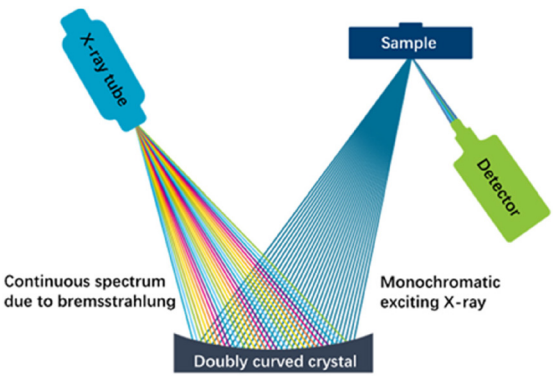

Fig. 1 Scheme of a monochromatic excitation energy dispersive X-ray fluorescence spectrometer equipped with a doubly curved crystal.

(Agilent Technologies Japan Ltd, Tokyo, Japan) was used for parallel analysis as the reference method (Table S1†). Target isotopes and the corresponding internal standards were ^{75}As (^{72}Ge), ^{111}Cd (^{115}In), and ^{208}Pb (^{209}Bi) from Agilent. The detection limits were determined as 0.002, 0.02, and 0.002 mg kg^{-1} for As, Pb, and Cd, respectively.

Method development and evaluation

The limit of detection (LoD) and the limit of quantification (LoQ) of HS-XRF were determined using two approaches. Then, the precision was evaluated with the quality control sample and seven herbal medicine samples for each element. Finally, the correlation between the HS-XRF and ICP-MS results and the accuracy were evaluated by examining all samples with heavy metal residues above the LoD for each element. Step-by-step details are discussed in the next section.

Results and discussion

Estimating detection limits using two approaches

A traditional approach to estimating the detection limit of a newly established/applied method relies solely on a blank sample or zero calibrator.[21] Ideally, for analyzing herbal medicines, real samples free of As, Pb, and Cd are needed to determine the matrix effect for each species. However, it is not feasible to obtain blank samples for the several hundreds of most frequently used herbal medicines. Instead, a more practical compromise would be a universal blank matrix broadly available and representative of most herbal medicines in terms of the major element content. In fact, the cell wall accounts for most of the dry weight of plants and 90 to 95 percent of the cell wall is composed of cellulose, hemicellulose, and lignin.[22] These three components all consist of hydrogen, carbon, and oxygen, and the elemental ratio of the cell wall in different herbal medicines varies due to their lignin content (20–25% dry weight).[22] Therefore, the most abundant content, cellulose, was selected as the "blank" in this study.

A typical approach to estimating the LoD and LoQ starts with measuring a designated number of replicates of blank samples to determine the mean value ($Mean_{blank}$) and standard deviation (SD_{mean}). Depending on the nature of raw signals, the LoD is calculated as the multiple (very often 3, commonly referred to as 3σ criterion) of SD_{blank} or $Mean_{blank}$ plus the assigned multiple of SD_{blank}. Since only positive values are generated *via* fast FP iteration, it is more appropriate to include $Mean_{blank}$ in the calculation. The LoD was estimated to be 0.049, 0.147, and 0.079 mg kg^{-1} for As, Pb, and Cd, respectively (Table 1). Similarly, the LoQ was estimated by adding 10 SD_{blank} to $Mean_{blank}$, which resulted in 0.138, 0.345, and 0.227 mg kg^{-1} for As, Pb, and Cd, respectively (Table 1). In this quick and straightforward estimation, the results determined by HS-XRF were generally 50–300% higher than the ICP-MS results for real samples with residue levels from 0 to 1.5 LoD and a high coefficient of variation (CV) in the HS-XRF values (more details later in this section). These observations may reflect the weakness of this estimation approach: the lack of objective evidence to prove that the signal produced by a low analyte concentration will indeed be distinguishable from that by blank samples.[21]

Table 1 Summary of detection limits estimated using different approaches

Parameter (method of calculation)	As conc.	Pb conc.	Cd conc.
$Mean_{blank}$ (n = 11)	0.010	0.062	0.016
SD_{blank}	0.013	0.028	0.021
$LoD_{traditional}$ (= $Mean_{blank}$ + 3 × SD_{blank})	0.049	0.147	0.079
$LoQ_{traditional}$ (= $Mean_{blank}$ + 10 × SD_{blank})	0.138	0.345	0.227
LoB ($Mean_{blank}$ + $t_{(95\%,\ 10)}$ × SD_{blank})	0.034	0.114	0.054
$SD_{low\ conc.\ sample}$ (n = 7)	0.031	0.061	0.031
$LoD_{alternative}$ (= LoB + $t_{(95\%,\ 6)}$ × $SD_{low\ conc.}$)	0.093	0.232	0.114
$LoQ_{alternative}$ (CV < 20%, −30% ≤ RD ≤ 30%)	≤0.264	≤0.299	≤0.252
Maximum residue level[12]	2	5	1

Concentration in mg kg^{-1}. SD: standard deviation. CV: coefficient of variation. RD: relative difference, referring to the ICP-MS result.

An alternative approach introduces samples with low but determined concentrations of analytes into the calculation. This approach requires, ideally, certified samples as the reference materials to determine a meaningful LoD conclusively. However, the availability of certified samples is far from satisfactory in both numbers and species. Furthermore, preparing artificially contaminated herbal samples is also highly challenging because it is not simply adding known concentrations of solutions to a blank extract like in the ICP-MS method. For producing samples that can represent the contamination pattern (*e.g.*, distribution, chemical form) in real-world situations, contaminants should be added during the growing stages of plants rather than after the post-harvest processing (*e.g.*, drying, slicing). Otherwise, the XRF signal response could be significantly affected. In this case, real samples with HS-XRF results close to the previous estimated LoD were analyzed using ICP-MS and then included as the objective data to compare with the blank (*i.e.*, cellulose).

In this alternative approach described in Table 1, the limit of blank (LoB) is introduced to present the highest *apparent* analyte expected to be found from analyte-free replicates, calculated by adding up $Mean_{blank}$ and 1.645 SD_{blank} (*i.e.*, 95% confidence level, two-tailed, infinite degrees of freedom). Then, $SD_{low\ conc.\ sample}$ from 7 replicates of each low concentration sample was used to determine $LoD_{alternative}$ (Table 1, $LoD_{alternative}$ = LoB + $t_{(95\%,\ df)}$ × $SD_{low\ conc.}$) to be 0.093, 0.232, and 0.114 mg kg^{-1} for As, Pb, and Cd, respectively. Although a high number of replicates are suggested, it was found that doubling sample numbers made very little difference in estimating the LoD for all three elements, from 0.093 to 0.089 for As, from 0.232 to 0.240 for Pb, and from 0.114 to 0.116 for Cd. For LoQ, this approach adopts more descriptive criteria to define this "functional sensitivity" instead of calculation.[21] $LoQ_{alternative}$ is assigned as the concentration that results in CVs less than a predetermined percentage (usually 20–30%),

thus reflecting the precision of the method at low analyte levels.

Precision, accuracy, and $LoQ_{alternative}$

Seven herbal medicine samples and the certified reference sample were measured seven times for each element so as to evaluate the precision of the proposed HS-XRF method (Table 2). These seven samples were selected based on the level of each heavy metal residue determined by ICP-MS, covering the concentration range from approximately 1 to 10 times of $LoD_{traditional}$. The relative difference (RD) of the HS-XRF result from the results determined by ICP-MS was then used to evaluate the accuracy, and the CV reflects the precision of this method.

Along with the increase in concentration level, both CVs and the absolute value of RDs decreased towards zero for all three elements as the general trend (Table 2). For As, both CV and RD were unacceptably high above $LoD_{traditional}$ (0.049 mg kg^{-1}) but below $LoD_{alternative}$ (0.093 mg kg^{-1}), which is likely a direct result of the matrix effect. Taking CV $\leq$ 20% and $-30\% \leq$ RD $\leq$ 30% as the criteria of "functional sensitivity", $LoQ_{alternative}$ should lie between 0.165 mg kg^{-1} (CV = 25%, RD = 9%) and 0.264 mg kg^{-1} (CV = 12%, RD = 5%). Such a concentration was only 1/10th to 1/8th of the MRL (2 mg kg^{-1}) so that this LoQ ($\leq$0.264 mg kg^{-1}) was meaningful. For Pb, the (absolute value of) RDs were less than 100% at the concentration below the $LoD_{alternative}$ and even the $LoD_{traditional}$, but the CVs still followed a similar trend to the As data. The $LoQ_{alternative}$ could be approximately 0.299 mg kg^{-1} with the same criteria.

Table 2 HS-XRF results for real herbal medicine samples

Element	Sample code	HS-XRF result	CV (n = 7)	ICP-MS result	RD
As	A01575	0.058	53%	0.022	164%
	A01225	0.070	45%	0.020	250%
	A01905	0.114	39%	0.104	10%
	A01170	0.160	24%	0.159	1%
	A01417	0.165	25%	0.152	9%
	QC	0.264	12%	0.252	5%
	A01365	0.277	17%	0.295	−6%
	A01477	0.577	5%	0.596	−3%
Pb	A00413	0.124	49%	0.072	72%
	A01905	0.170	41%	0.124	37%
	A01225	0.165	31%	0.197	−16%
	A01170	0.251	27%	0.238	5%
	A01575	0.299	18%	0.376	−20%
	QC	0.504	13%	0.570	−12%
	A01365	1.030	7%	1.209	−15%
	A01913	1.320	5%	1.188	11%
Cd	A01170	0.061	53%	0.016	281%
	A01905	0.075	41%	0.029	159%
	A01365	0.100	26%	0.120	−17%
	A01225	0.252	12%	0.223	13%
	A01913	0.258	9%	0.286	−10%
	A00413	0.293	14%	0.259	13%
	QC	0.583	4%	0.67	−13%
	A01575	0.608	7%	0.661	−8%

Concentration results in mg kg^{-1}. CV: coefficient of variation. RD: relative difference, referring to the ICP-MS result.

For Cd, CVs and RDs followed the same trend as the As data so that the same criteria were still effective (with an additional rule: LoD $\leq$ LoQ[21]). Thus, the $LoQ_{alternative}$ should lie between 0.114 mg kg^{-1} ($LoD_{alternative}$) and 0.264 mg kg^{-1} (CV = 12%, RD = 13%), which is comparable to the performance reported in the only previous study (LoD = 0.083 mg kg^{-1}, LoQ = 0.207 mg kg^{-1}).[16] For all three elements, the RDs get smaller as the concentration rises, implying an increase in the accuracy of the HS-XRF method. This result follows the trend described by the Horwitz equation,[23] under which the predicted CVs are 16%, 14% and 15% for $LoD_{alternative}$, close to the CV for $LoQ_{alternative}$. However, it is still not safe to draw an intuitive and empirical conclusion based on only 8 samples in each element.

Correlation between HS-XRF and ICP-MS results

To further examine the accuracy of the HS-XRF method, heavy metal residues in all 99 real herbal medicine samples were determined by HS-XRF and ICP-MS in parallel. Among 99 pairs of the results, all those below the $LoD_{alternative}$ were ruled out. The remaining pairs (52, 50, and 29, including potential outliers) were analyzed *via* linear regression and the associated assumption test (Fig. 2).

In general, the HS-XRF results fit the ICP-MS result with a linear relation for all three elements. R^2 were calculated to be 0.9059, 0.9612, and 0.9631 for As, Pb, and Cd, respectively. The standard residues of each regression passed the Shapiro–Wilk test although the p-values were not dominantly higher than 0.05 but only 0.18, 0.24, and 0.15 for As, Pb, and Cd, respectively. The relatively low p-values were likely affected by the small absolute difference between the two methods at low concentrations, especially between one and two times the LoD. Another possibility is that the absolute difference at higher concentrations (*e.g.*, 3 LoD and higher) still increases slowly and thus the standardized residues tend to form a bell shape while the relative difference decreases slowly. Referring to the ICP-MS method, the HS-XRF method's performance on Pb and Cd is better than that on As, in terms of the systematic errors. For As, the HS-XRF results are proportionally lower but constantly higher than the ICP-MS results (slope = 0.9265, $p \ll 0.05$; intercept = 0.0288, p = 0.02). For Pb and Cd, the HS-XRF results are very close to the reference method (slope = 0.9818 and 0.9901; both $p \ll 0.05$) with no significant constant errors (intercept = −0.0129 and −0.0073; p = 0.57 and 0.63). Regardless, as predicted in the criteria of $LoQ_{alternative}$, all 131 RDs were within the range of −30% and 30% with one exception/outlier in the Cd group (HS-XRF = 0.32 mg kg^{-1}, ICP-MS = 0.207 mg kg^{-1}, RD = −35%). A paired t-test (two-tailed, 95% confidence level) was also performed for the above-LoD result pairs assuming the normal distribution of the data. Only for Pb there was a small difference, −0.025 mg kg^{-1} (p = 0.045), approximately 1/10th of the $LoD_{alternative}$ (0.232 mg kg^{-1}) and 1/200th of the MRL (5 mg kg^{-1}).

In brief, the HS-XRF method could determine the concentration of As, Pb, and Cd in real herbal medicine samples and the results fitted to that determined by the reference method of ICP-MS. The overall performance of HS-XRF is sufficient for

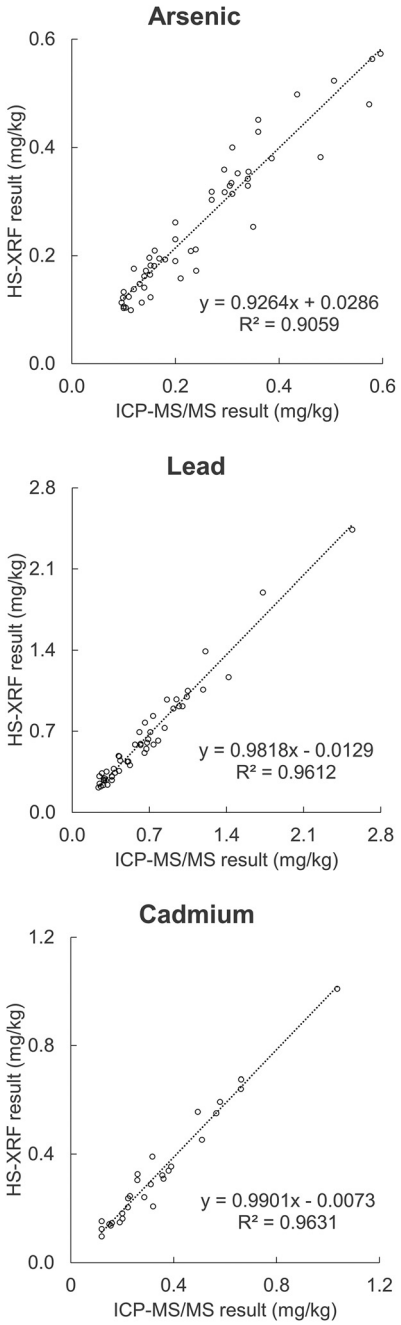

Fig. 2 Correlation between the HS-XRF and ICP-MS/MS results above the $LoD_{alternative}$ (52, 50, and 29 pairs for As, Pb, and Cd; no outlier ruled out).

quantification though ICP-MS is still recommended for critical concentrations (*i.e.*, close to MRL). Compared with the traditional approach, the alternative approach estimated the LoD and LoQ more conservatively but may better reduce the risk of potential bias (*e.g.*, non-normal distribution).

Towards practical application scenarios

Compared with ICP-MS, HS-XRF is a rapid, low-cost and easy-to-use approach to determine heavy metal residues in Chinese herbal medicines. All equipment needed for the entire method is only a blender, a pressor, and an XRF spectrometer, all portable and requiring no laboratory settings. Sample preparation takes less than 5 min, and the XRF analysis for all three elements lasts 10–20 min (depending on the sample) with no complicated operation required. Since the only major investment is the XRF spectrometer (*e.g.*, purchasing, renting, or sharing), the overall cost per sample could be reduced to only 1/10th to 1/5th of that for ICP-MS. Therefore, the HS-XRF method demonstrates the potential to establish a rapid screening protocol to determine heavy metal residues in Chinese herbal medicines. Here, we propose two scenarios based on our experience in routine tests at the regulatory agencies and communication with the communities and commercial end-users.

At the regulatory agencies (*e.g.*, customs, food and drug administration), rapid and high-throughput screening of heavy metal residues is in high demand in handling a large number of samples of different herbal species from various sources. For both routine tests and surveillances of special interest, ICP-MS and AAS methods limit the testing capacity, thus weakening the market monitoring power. Adopting HS-XRF as a pre-screening method might greatly provide the capacity for more critical and challenging tests. For instance, considering the specific situation and functional sensitivity of HS-XFR, samples with a concentration (by HS-XFR) higher than a certain percental of MRL (*e.g.*, 60–70%) are subjected to further analysis by ICP-MS. Such options may speed up the routine test at customs and better serve time-sensitive requests, such as community services and import/export certification.

The other scenario is the demand for on-site service. Herbal medicine markets, especially the growing number of trade centers near the origin of medical herbs,[24] are typically far away from complete facilities that are more available in large cities. Both suppliers and buyers demand rapid, on-site screening in high-efficiency trade. Similarly, due to the batch-to-batch variations among the raw herbs provided by different growers and harvesters on a small scale in rural areas, the procurement personnel from the processing company often risk failing more raw materials due to batch-mixing and limited numbers of sample testing. Portable equipment and low-cost testing may improve the purchasing procedure at the origin place of medicinal herbs, thus reducing the risk of distributing contaminated products from the source.

Conclusions

This study established and evaluated an HS-XRF method for rapid detection and quantification of As, Pb, and Cd in traditional Chinese herbal medicines. The LoD was determined to be 0.093, 0.232, and 0.114 mg kg^{-1} for As, Pb, and Cd, respectively, using the more conservative approach. With more herbal medicine samples, the precision was evaluated to estimate the functional sensitivity (*i.e.*, LoQ), and the accuracy was

examined *via* regression between the HS-XRF results and the concentration determined by ICP-MS. We also proposed real-world scenarios where this rapid, low-cost and easy-to-use HS-XRF method could fit into practical applications based on our experience in regulatory tests and service to the community. With more improvement and data, HS-XRF would improve the testing efficiency and reform the routine analysis structure, making a great contribution to monitoring heavy metal contamination in herbal medicines.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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