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Paper

Heavy metals and probabilistic risk assessment via *Prunella vulgaris* (food and medicine homology) consumption in Guangdong Province, China

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***Prunella vulgaris* is widely used as the main ingredient of herb tea in Southeast Asia, as well as a traditional Chinese medicine. However, the heavy metal contaminations such as arsenic, cadmium, mercury and lead in *P. vulgaris* may be a cause for concern due to the environment pollution around, plantation and processing contamination. Thus, this study intented to assess both non-carcinogenic risks and carcinogenic risks attributed to cumulative exposure to the four heavy metals in *P. vulgaris*. The contaminations levels of heavy metals were determined in 90 batches of *P. vulgaris*. And the consumption level was obtained through a questionnaire survey among a total of 6,235 adult participants in Guangdong province. This study estimated the probabilistic health risks using Monte Carlo simulation, and found that the estimated mean and the 95th percentile values for cumulative noncarcinogenic risk (HI value) and carcinogenic risk (TCR value) of *P. vulgaris* were all within the acceptable risk. And the assessment results indicated that arsenic was the primary contributors to both noncarcinogenic and carcinogenic risks through *P. vulgaris* consumption. These findings and continuing the surveillance of heavy metals in *P. vulgaris* will be particularly relevant to both consumers and policy makers.**

Key words: *Prunella vulgaris*; food and medicine homology; heavy metals; probabilistic risk assessments; @risk.

Introduction

P. vulgaris, belonging to Lamiaceae family Prunella genus, is food and medicine homologic. *P. vulgaris* is widely used as traditional Chinese medicine and the main ingredient of herb tea in Southeast Asia. According to the Chinese Pharmacopoeia compiled by the Pharmacopoeia Commission of the People's Republic of China (2020),[1] the dried fruit spike of *P. vulgaris* has effects of sedation, antifebrile and detumescence. *P. vulgaris can be* used for the treatment of mastitis, thyroid gland malfunction, pulmonary tuberculosis and so on.[2,3] In recent years, the market demand for *P. vulgaris* has been increasing both domestically and internationally. It is thus a trend to develop the artificial standardized cultivation of *P. vulgaris*. However, heavy metal contamination has become an important issue that urgently needs to be solved in the production and preparation of traditional Chinese medicine.[4] The World Health Organization (WHO) and Food and Agriculture Organization of the United Nations (FAO) recommends that foods as well as medicinal herbs should be assessed for safety, prompting the medicinal herbs and food ingredient are safe for consumers.[5]

Some studies have found that lead pollution in *P. vulgaris* is serious.[2,6] However, the research on the safety of *P. vulgaris* intaking is still in its early stages. There is an urgent need to conduct quantitative risk assessment of different pollutants through the consumption of *P. vulgaris*. Health risk assessment is widely used to quantitatively estimate the probability and the probable degree of pollutants on human health.[7,8] Health risk assessment included non-carcinogenic and carcinogenic risks. And probabilistic analysis with Monte Carlo simulation is recognized to decrease the uncertainty of food safety risk assessment.[9]

Therefore, the objective of this study were 1) to determine the multiple heavy metal concentrations and the actual consumption characteristics of *P. vulgaris* in Guangdong province, a typical region having a developed economy and high level of industrialization in South China, 2) to conduct the probabilistic risk assessment of heavy metals via the consumption of *P. vulgaris*, and 3) to provide scientific basis for consumption instruction of *P. vulgaris*.

Materials and methods

Participants and samples

The consumption data of *P. vulgaris* were from a special investigation from 2019 to 2021. The participants were selected by the multistage random cluster sampling method. All of the 6,235 subjects (3,069 males and 3,166 females) included in this study were randomly recruited. The subjects involved in these investigation were 18 years or older, and their names have been anonymized. All participants were informed of the objective of this investigation and signatured the informed consent

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forms. Each participant was required to answer a demographic information questionnaire (including occupation, education condition, etc.) and *P. vulgaris* consumption frequency was asked during the last 12 months before receiving the questionnaire survey, as well as measure height and weight. The questionnaire investigation was conducted by our investigators going door to door. All the consumption information was double input into computer with the EpiData software by two professionals.

To determine the heavy metal contaminations in *P. vulgaris*, 90 samples of *P. vulgaris* were collected from different pharmacies and markets in Guangdong (30 samples from each of the three cities of Guangzhou, Zhongshan and Yunfu) between 2022 and 2023. And no more than 3 samples should be collected from the same pharmacy or market. All the samples were kept dry in food grade moisture-proof plastic bags at 4 °C before analysis.

Samples pre-treatment and analysis

To investigate arsenic (As), cadmium (Cd), mercury (Hg) and lead (Pb) concentrations in *P. vulgaris* of Guangdong province in China, all the 90 samples were determined by Inductively Coupled Plasma Mass Spectrometry (ICP-MS, Agilent 7900, USA) after closedvessel microwave digestion procedures, according to the Chinese National Food Safety Standard of determination of multi-elements in food (GB 5009.268-2016). Each sample was crushed by the high speed crusher Tnc5200 (Vitamix, USA) and collected in food grade sealed plastic bags individually for later use. 0.3 g of each evenly crushed *P. vulgaris* sample was weighed and digested in 8 ml of HNO_3 (65%, with the purity of ppb level) by microwave digestion system (UltraCLAVE, Italy). After digesting for a hour, the heating program was used by the microwave digestion system. Then the prepared samples were holding for 30 min at 100 °C and diluted to 50.00 ml with Milli-Q water and then tested by ICP-MS. The limit of detections (LODs) were 0.02, 0.002, 0.002, and 0.001 mg/kg, and the limit of quantitations (LOQs) were 0.05, 0.005, 0.005, and 0.003 mg/kg for Pb, Cd, As, and Hg, respectively. Quality control procedures were conducted strictly. A solution blank and two quality control samples were run in each batch to check for contamination, response value, and accurate quantification. During the instrumental analysis, a standard solution and a reference material sample were inserted after every 20 samples. To check the reproducibility of the method, a paralleled sample was tested after every 10 samples.

Health risk assessment of heavy metal

Estimated daily intake (EDI)

The EDI of heavy metals in *P. vulgaris* was calculated according to the guidance of USEPA and FAO/WHO and expressed in μg/kg bw/d.[5,8] In equation (1), F is the *P. vulgaris* daily intake (g/day per person), C is the concentration of a certain heavy metal in *P. vulgaris* (mg/kg), and BW is the body weight (kg).

$$EDI = \frac{F \times C}{BW} \tag{1}$$

Non-carcinogenic risks of cumulative exposure to heavy metals

The non-carcinogenic risks for each individual metal (Pb, Cd, As or Hg) were assessed using the hazard quotient (HQ). The cumulative risk assessment were calculated using hazard index(HI)approach. In Equation (2), RfD is the reference dose of the heavy metal, which is 3.5, 1.0, 0.3 and 0.3 μg/kg/d for Pb, Cd, As and Hg, respectively.[4,8] If the HI value is equal or < 1, the non-carcinogenic risk is very low.

$$HQ = \frac{EDI}{RfD} \tag{2}$$

$$HI = \sum HQ \tag{3}$$

Carcinogenic risks of cumulative exposure to heavy metals

The Lifetime Cancer Risk of individual metal is generally characterized by Carcinogenic Risk (CR). And the Total Carcinogenic Risk (TCR) is taken as measure of carcinogenic risk through combined exposure to multiple heavy metals and harmful elements. In equations (4), CSF represents the oral carcinogenic slope factor, which is 0.38×10^{-3}, 0.85×10^{-5}, 1.5×10^{-3} kg·d/μg for Cd, Pb, and As, respectively.[10,11] Moverover, no human data currently are available to indicate that mercury exposure can lead to cancer.[12] The tolerable CR standard is 10^{-6} to 10^{-4}.[13–15]

$$CR = EDI \times CSF \tag{4}$$

$$TCR = \sum CR \tag{5}$$

Statistical analysis

Concentration values below the LODs were reported as not detected and replaced by zero for statistical analysis.[16] SAS Enterprise Guide (SAS Institute Inc., Cary, NC, USA) were utilized to conduct the statistical analyses of consumption characteristics of *P. vulgaris*. For probabilistic risk assessment, Monte Carlo simulation was performed for both contaminant concentrations and consumption levels of *P. vulgaris*. And 10,000 iterations were conducted to quantify the uncertainty of risk assessment using the latin hypercube sampling method. The probability distribution of the desired parameters were analyzed using @RISK 8.x - Idustrial software (Palisade, USA).

Results and discussion

Consumption characteristics of *P. vulgaris*

Among the total 6,235 participants, 1,384 participants had ate *P. vulgaris* during the last 12 months. Thus the consumption rate of *P. vulgaris* for human in Guangdong Province was 22.2%. And the 1,384 participants who had ate *P. vulgaris* were considered to be the consumer group. The daily dietary consumption of *P. vulgaris* for both the consumer group and the total participants was summarized (Table 1). The mean and 95th percentile (P95) of daily consumption of *P. vulgaris* intake for the total participants were 0.12 and 0.60 g/day per person, respectively. The mean and P95 of daily consumption for the consumer group were 0.52 and 2.00 g/day per person, respectively. The investigated consumption level for the population of Guangdong province was far below the medicinal limit range of 9 to 15 g/day per person for *P. vulgaris* in Chinese Pharmacopoeia. *P. vulgaris* is widely used as food and medicine homologous substance in Southeast Asia, especially used as the main ingredient of herb tea in south China.[17]

Concentrations of heavy metals in *P. vulgaris* samples

The mean concentration values of Pb, As, Cd and Hg were 0.917, 0.129, 0.046 and 0.003 mg/kg, respectively, with the P95 values of 2.310, 0.277, 0.068 and 0.010 mg/kg, respectively (Table 2). The

Table 1. Daily consumptions of *Prunella vulgaris* in both consumer group and the total participants according to the dietary survey (g/day per person).

Group	Number of Participants	Body Weight (mean, kg)	BMI (mean, kg/m ^{2})	Daily consumption (g/day per person)		
				Mean	P50	P5–P95
Consumer Group	1,384	60.96	22.76	0.52	0.17	0.025–2.00
The Total Participants	6,235	60.95	22.74	0.12	0	0–0.60

Table 2. Heavy metal pollution in *Prunella vulgaris* (mg/kg).

Metal	Mean	SD [a]	Min	Max	Median	P95
Pb	0.917	0.491	0.353	6.230	0.632	2.310
Cd	0.046	0.012	0.016	0.107	0.043	0.068
As	0.129	0.042	0.041	0.320	0.114	0.277
Hg	0.003	0.004	0.000	0.040	0.000	0.010

[a]SD represents standard deviation.

contamination levels were found in the orde of Pb > As > Cd > Hg. The investigated concentration levels of Pb, As, Cd and Hg for *P. vulgaris* were lower than the studys in other regions of China.[9,18] The detection ratios of As, Pb and Cd were all 100%, while the detection ratio of Hg was 33.33%. Referring to the explicit limits of 5.0, 1.0, 2.0, 0.2 mg/kg for Pb, Cd, As and Hg, respectively in the Chinese Pharmacopoeia, there was only one sample exceeding the limit of Pb, while the other samples did not exceed the standard. However, the above limits of heavy metals are only for medicinal limit of *P. vulgaris*. *P. vulgaris* can also be consumed especially as the herb tea.

Probabilistic health risk assessment of heavy metal via *P. vulgaris* consumption

Exposure to heavy metals from P. vulgaris consumption

With the probability distribution of the heavy metal concentration and *P. vulgaris* consumption, Monte Carlo simulation was conducted to quantify the uncertainty in the health risk assessments. The probability distributions were simulated through 100,00 iterations. On account of more conservative approachs, the value of consumption data was randomly selected from the dataset of *P. vulgaris* consumer Group. Calculated EDI of four heavy metals exposure through *P. vulgaris* consumption is summarizes in Table 3. And the health guidance values recommended by WHO/FAO expert committee are also depicted. The provisional tolerable monthly intake (PTMI) for Cd was set at 25 μg/kg bw/month, basing on the kidney toxicity effects of Cd.[5] For adults, the Point of departure of Pb is 1.2 μg/kg bw/d, for 1 mm Hg increase in blood pressure.[12] The provisional tolerable weekly intake (PTWI) value of 4 μg/kg bw/week, was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish.[12] The inorganic arsenic lower limit on the benchmark dose for a 0.5% ($BMDL_{0.5}$) increased lung cancer incidence was 3 μg/kg bw/d.[12] It was more conservative to assume all the As speciation in the present research were the most toxic inorganic forms.

As shown in Table 3, the EDI values of the four heavy metals involved in the evaluation are all lower than their Health Guidance Values, respectively. In detail, the estimated mean of the EDI value for Pb, As, Cd and Hg under the consumption of *P. vulgaris* by adult was 0.750×10^{-2}, 1.061×10^{-3}, 0.383×10^{-3}, 0.286×10^{-4} μg/kg bw/d, respectively. They were found in the orde of Pb > As > Cd > Hg, which was similar to that detected in other traditional chinese herbal medicines.[9,19,20]

Non-carcinogenic risk assessment of cumulative exposure to heavy metals

In base of Monte Carlo simulation through 100,00 iterations, the calculated HQ and HI results for accessing non-carcinogenic risks of As, Pb, Cd and Hg are listed in Table 4. The highest mean value of HQ was As (0.214×10^{-2}), while the lowest was for Hg (0.095×10^{-3}). Among the determined heavy metals, the P95 of HQ values for As, Pb, Cd and Hg were 1.333×10^{-2}, 0.799×10^{-2}, 0.135×10^{-2} and 0.384×10^{-3}, respectively. The mean and the P95 values of simulated HQ of all studied elements for *P. vulgaris* were followed the decreasing order of As > Pb > Cd > Hg, which was consistent with that of heavy metals in agricultural soil of china.[21,22] As show in Table 4 and Fig. 1, the estimated mean HI value for the four elements of *P. vulgaris* was 0.006, and the P95 of HI value was 0.023, which were both lower than 1, indicating that the cumulative exposure to the four heavy metals through *P. vulgaris* consumption was within the acceptable range.

Carcinogenic risk assessment of cumulative exposure to heavy metals

In addition, the heavy metals of As, Pb, and Cd exhibited carcinogenic toxicity. The CR values and TCR were calculated and compared with the acceptable TCR value (1×10^{-4}) stated by USEPA.[14] It was proposed that the general exposure to methylmercury and inorganic mercury may not cause human cancer.[8] It was concluded that the evidence for carcinogenicity of inorganic arsenic compounds in experimental animals is sufficient by IARC. Inorganic arsenic induces bladder and lung tumours in experimental animals.[12] As shown in Table 5 and Fig. 2, the mean levels for CR of *P. vulgaris* were observed in the order of As > Cd > Pb. The estimated mean and the P95 values for CR of individual heavy metals and the TCR of cumulative exposure were within the tolerable range. And it was indicated that As was the primary contributors to carcinogenic risks in *P. vulgaris*, which was consistent with the related research of other Chinese traditional medicines.[23] Therefore, it is necessary to take special attention to reduce these heavy metals, especially for As in *P. vulgaris*.

Conclusion

This study investigated concentrations of As, Pb, Cd and Hg in 90 batches of *P. vulgaris* samples collected from Guangdong Province between 2022 and 2023. And the consumption data were from

Table 3. Health guidance values and EDIs of heavy metals attributed to *Prunella vulgaris* consumption for male and female *P. vulgaris* consumer population (≥ 18 years) in Guangdong Province, China.

Metal	*P. vulgaris* Consumer population	EDI (μg/kg bw/d)			Health Guidance Values (μg/kg bw/d)
		Mean	Median	P95	
Pb	Male	0.764×10^{-2}	0.205×10^{-2}	2.640×10^{-2}	1.2 ($BMDL_{10}$)[a]
	Female	0.740×10^{-2}	0.223×10^{-2}	2.810×10^{-2}	
	Total	0.750×10^{-2}	0.216×10^{-2}	2.798×10^{-2}	
Cd	Male	0.380×10^{-3}	0.119×10^{-3}	1.325×10^{-3}	0.833[b]
	Female	0.382×10^{-3}	0.134×10^{-3}	1.410×10^{-3}	
	Total	0.383×10^{-3}	0.128×10^{-3}	1.353×10^{-3}	
As	Male	1.080×10^{-3}	0.330×10^{-3}	3.730×10^{-3}	3 ($BMDL_{0.5}$)[c]
	Female	1.085×10^{-3}	0.372×10^{-3}	4.117×10^{-3}	
	Total	1.061×10^{-3}	0.351×10^{-3}	3.998×10^{-3}	
Hg	Male	0.277×10^{-4}	0.054×10^{-4}	1.074×10^{-4}	0.571[d]
	Female	0.301×10^{-4}	0.059×10^{-4}	1.138×10^{-4}	
	Total	0.286×10^{-4}	0.056×10^{-4}	1.151×10^{-4}	

[a]The lower limit on the benchmark dose (FAO/WHO, 2011).[12] [b]Converted by the provisional tolerable monthly intake (PTMI) of 25 μg/kg bw/Month (FAO/WHO, 2023).[5] [c]The inorganic arsenic lower limit on the benchmark dose (FAO/WHO, 2011).[12] [d]Converted by the provisional tolerable weekly intake (PTWI) of 4 μg/kg bw/Month (FAO/WHO, 2011).[12]

Table 4. Probabilistic estimation of HQ and calculated HI for the investigated heavy metals of *Prunella vulgaris* consumer population.

Metal	HQ					Contribution of HI (%)	HI (Mean)
	Mean	Median	P95	Minimum	Maximum		
Pb	0.214×10^{-2}	0.062×10^{-2}	0.799×10^{-2}	0.381×10^{-5}	0.162	34.74	0.006
Cd	0.384×10^{-3}	0.013×10^{-2}	0.135×10^{-2}	0.061×10^{-5}	0.026	6.22	
As	0.354×10^{-2}	0.117×10^{-2}	1.333×10^{-2}	0.507×10^{-5}	0.197	57.47	
Hg	0.095×10^{-3}	0.019×10^{-3}	0.384×10^{-3}	0.013×10^{-5}	0.010	1.55	

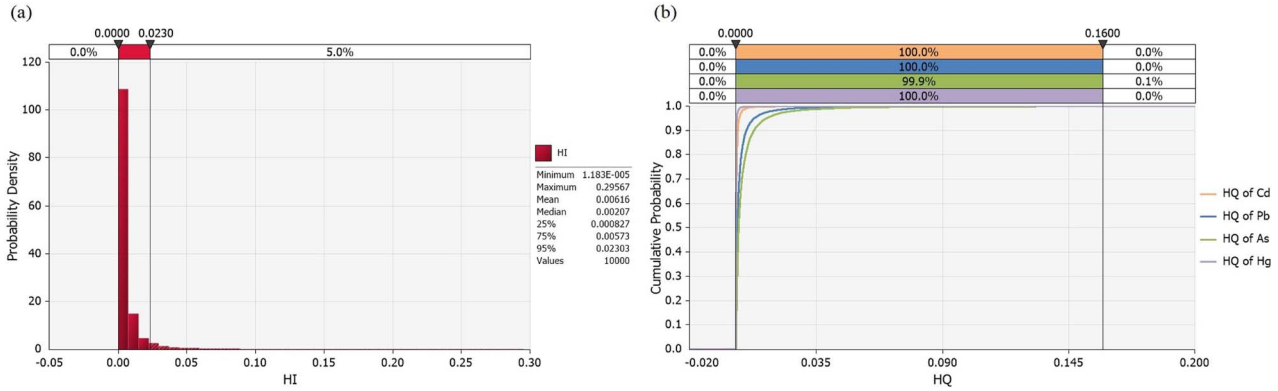

Fig. 1. Probabilistic noncarcinogenic risk levels of individual (HQ values) and cumulative (HI value) exposure to the selected heavy metals through *Prunella vulgaris* consumption for adults in Guangdong Province, China. a) HI values of four heavy metals in *P. vulgaris*. b) HQ values of Cd, Pb, As and Hg in *P. vulgaris*.

Table 5. Probabilistic estimation of CR and calculated TCR of toxic elements of *Prunella vulgaris* consumer population.

Metal	CR					Contribution of TCR (%)	TCR (Mean)
	Mean	Median	P95	Minimum	Maximum		
Pb	0.630×10^{-7}	0.179×10^{-7}	2.342×10^{-7}	0.001×10^{-7}	8.639×10^{-6}	3.39	1.860×10^{-6}
Cd	0.148×10^{-6}	0.487×10^{-7}	0.525×10^{-6}	0.003×10^{-7}	1.033×10^{-5}	7.96	
As	0.165×10^{-5}	0.531×10^{-6}	0.599×10^{-5}	0.023×10^{-7}	2.231×10^{-4}	88.71	

a special investigation of *P. vulgaris* from 2019 to 2021,which firstly provided actual consumption characteristics of the general population in Guangdong province. This study found that the mean and P95 of daily consumption for the *P. vulgaris* consumer group of Guangdong province were 0.52 and 2.00 g/day per person, respectively. In particular, the probabilistic risk assessment of both non-carcinogenic and carcinogenic risks was conducted to evaluate the health risk attributed to cumulative exposure to the four heavy metals in *P. vulgaris*. The findings clearly found that the mean concentrations of heavy metals in *P. vulgaris* were observed

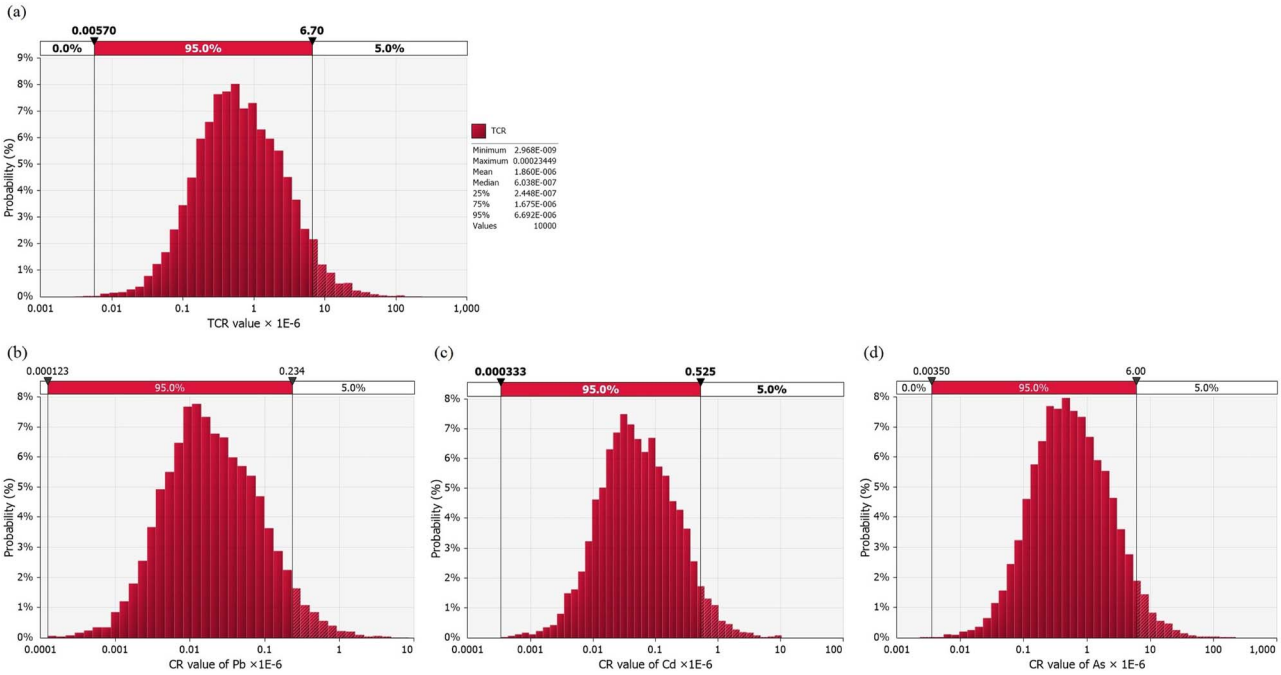

Fig. 2. Probabilistic carcinogenic risk levels of individual (CR values) and cumulative (TCR value) exposure to the selected heavy metals through *Prunella vulgaris* consumption for adults in Guangdong Province, China. a) TCR values of cumulative exposure to the three heavy metals in *P. vulgaris*. b) c) and d) CR values of Pb, Cd and As in *P. vulgaris*.

in the descending order of Pb > As > Cd > Hg, while the simulated HQ values of all studied elements for *P. vulgaris* were followed the order of As > Pb > Cd > Hg. For adults, the probabilistic risk assessment showed that the estimated mean and the P95 values for cumulative noncarcinogenic risk (HI value) and carcinogenic risk (TCR value) of *P. vulgaris* were all within the acceptable range under the actual consumption levels. And it was regarded that As was the primary contributors to both noncarcinogenic and carcinogenic risks through *P. vulgaris* consumption for adults in Guangdong Province, China. It thus indicated that it was necessary to take special attention on the reduction in As contamination, by avoiding the cultivation processes, harvesting process, storage, and transportation. There are few studies on the risk assessment of heavy metals via traditional food and medicine homologous substances, especially the *P. vulgaris*, which is widely used in Southeast Asia including the south of China. It is also necessary to comprehensively consider the dual attributes of both food and medicine, thus developing more reasonable limit standards for the food and medicine homologous substances. These findings and continuing the surveillance of heavy metals in *P. vulgaris* will be particularly relevant to both consumers and policy makers.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Rui Huang, Shaowei Chen, Zihui Chen, Ping Wang and Jiewen Peng. The first draft of the manuscript was written by Rui Huang. All authors have commented on previous versions of the manuscrip, tread and approved the final manuscript.

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Conflict of interest statement. The authors declare no conflict of interest.

Ethics approval and consent

This study was performed in accordance with the Declaration of Helsinki. The research involving human participants underwent a thorough review and obtained approval from the Ethical Committee of the Guangdong Provincial Center for Disease Control and Prevention. This study involved a questionnaire survey and did not involve any intervention measures. Before being included in the study, all participants provided explicit and written consent after being fully informed of the study's objectives and procedures.

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