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Probabilistic Framework for Assessing the Potential Human Risk of Heavy Metals in Chinese Herbal Medicine

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Abstract:*Chinese herbal medicine (CHM), widely used therapeutic agents for various purposes, contains abundant vitamins and specific compounds. Heavy metals in CHM may have adverse health effects. Heavy-metal concentrations of inorganic arsenic (iAs), cadmium (Cd), copper (Cu), mercury (Hg), and lead (Pb) in CHM prescriptions are obtained from the Taiwan Food and Drug Administration and the Herbal Pharmacopeia. The average daily intake of the Taiwanese population above 18 years old is used in the exposure assessment. In conclusion, the non-carcinogenic risk posed by iAs, Cd, Cu, Hg and Pb are within the acceptable safety range for human health, and the carcinogenic risk posed by iAs is also acceptable. Only the 95th percentile (P95) with prescription "Blood/Painkiller" (BP) of Hg is higher than 1, with a value of 1.7. The safety of CHM can be improved by Good Agricultural Practice (GAP) and Good Manufacture Practice (GMP), and by reducing the heavy-metal levels in the environment as possible. Further study can focus on vulnerable groups such as the elderly, children, pregnant or high-risk groups (patients using CHM in the long term).*

Keyword:*Health Risk Assessment, Heavy metal, Traditional Chinese Medicine.*

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I. Introduction

Traditional Chinese Medicine (TCM) has been used for centuries in the treatment of various ailments of Taiwanese. TCM has less side effects than western medicine [1]. Chinese Herbal Medicines (CHM) comprises the majority of treatments in TCM. CHM is composed of different ingredients, such as prescriptive botanicals, animal tissues, and minerals. There are some concerns about raw materials of CHM, specifically, the potential toxicity of plants, animal parts, and minerals. Heavy metals are the most common contaminants that are likely to be found in herbal materials or herbal products. Heavy metals in medicines may accumulate in organisms, leading to serious health hazards such as kidney injury, chronic toxicity symptoms, renal failure, and liver damage. Heavy metals such as mercury, lead, arsenic, and cadmium have previously been reported to be found in TCM [2,3]. In 251 CHM products collected from California herbal retail stores, 35 products contain mercury, 36 contain arsenic, and 24 contain lead, while at least 32% of the samples contain heavy metals [4].

Inorganic arsenic (iAs), cadmium (Cd), mercury (Hg), lead (Pb), and copper (Cu) are naturally occurring metals. Poisoning due to the use of CHM is common in Asia. Lead poisoning after the use of herbal medicines such as Bao-Ning-Dan (a kind of Chinese herbal pill) and Cordyceps have been reported [5-8]. In addition, inorganic arsenic poisoning (iAs) is found in anti-asthmatic herbal preparations [9]. Mercury and lead poisoning related to CHM in western countries have also been documented [10,11]. Heavy metals could be added intentionally for alleged medicinal purposes.

The International Agency for Research on Cancer has classified these metals into difference groups. iAs (arsenite As^{III} and arsenate As^{V}) and Cd are in group 1 and are human carcinogens. Pb is in group 2B and is possibly carcinogenic to humans. iAs is ranked first in the Agency for Toxic Substances and Disease Registry (ATSDR) priority list of hazardous substances in 2013 and 2015. Besides copper (118^{th}), other heavy metals are also ranked in the top ten [12,13]. Heavy-metal-contaminated CHM may pose serious risk to human health; therefore, the assessment potential human risk of heavy metals in TCM is important. The aim of this study is to assess the carcinogenic and non-carcinogenic risk posed by heavy metals in CHM prescription, including iAs, Cd, Cu, Hg, and Pb.

II. Material and Methods

2.1 Hazard Identification

Human epidemiological studies have been shown iAs to have potential to cause cancers, including lung cancer, bladder cancer, and skin cancer [14]. Chen et al. in 2010 conducted an epidemiological study of arsenic in Taiwan [15,16]. The subjects were adults aged 40 and over, and the iAs exposure source was drinking water. The critical endpoints were lung cancer and bladder cancer. The results of the study were used for determining the critical endpoint dose. Ahsan et al. conducted an epidemiological investigation into the relationship between exposure to iAs-contaminated well water and the incidence of skin cancer [17]. The research findings were used to assess the critical endpoint dose for skin cancer. All of the above studies provide human epidemiological data and confirm that iAs exposure has carcinogenic potential for humans. In addition, some non-carcinogenic potentials also were induced by iAs exposure, include skin lesion, cardiovascular outcomes and Black Foot Disease (BFD) [18].

The main sources of Pb include environmental and industrial pollution, and contamination during food processing. Pb has neurodevelopmental effects on children, and it raises the Systolic Blood Pressure (SBP) in adults. In 2011, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) reassessed the provisional tolerable weekly intake (PTWI) of Pb (previously 25 μg/kg bw/weekly) [18]. The results show that exposure to this level of PTWI reduces Intelligence Quotient (IQ) in children by 3-units and increases SBP in adults by 3 mm Hg. Therefore, the PTWI was found to be inappropriate for current exposure conditions and was subsequently revoked [18]. According to epidemiological investigations, the exposure level of Pb for a 1-unit reduction in children's IQ is 0.6 μg/kg bw/day [19], and the level for SBP to increase in adults is 1.3 μg/kg bw/day [20-23]. These findings were used as a basis to establish Health-Based Guidance Values (HBGV) for both children and adults.

Hg is naturally present in the environment, and methylmercury is its most toxic form. The highest concentrations of mercury are found in aquatic products; the relationship between Hg content and disease can be extrapolated from aquatic food intake or analyzed concentration of blood and hair. Animal experiments of National Toxicology Program study (NTP) were conducted using rats [24]. Exposure to drinking water containing increased renal Hg concentrations and changes in kidney weight. The benchmark dose lower confidence limit for a 10% (BMDL10) for the relative kidney weight gain in male rats was 0.11 mg HgCl/kg bw/day, which is equivalent to 0.06 mg Hg/kg bw/day, a value used for calculating HBGV.

Cu is an essential trace element in the human body; it plays an important role in the enzyme system, hematopoiesis, and cell metabolism. However, excessive copper can cause health problems. Shanaman et al. conducted a 1-year Cu experiment exposing male and female beagles to doses of 0.012%, 0.06%, and 0.24% [25]. High levels of accumulated Cu were found in the kidney and spleen. Twelve weeks after the exposure, this phenomenon vanished, and no deaths or significant pathological symptoms occurred. Research data on nutrition provided by the National Research Council, United States (NRC) in 1980 show that adults require 2-3 mg/day of Cu [26]. On the basis of these two studies, JECFA established the provisional maximum tolerable daily intake (PMTDI) for Cu [27].

Cd has been shown by an epidemiological investigation to have toxic effects on the kidneys, liver, and bones. Because of its bioaccumulation and long half-life, Cd may accumulate in the human kidney and liver following exposure, causing harm and leading to kidney dysfunction, skeletal damage, and itai-itai disease [28]. In 2013, JECFA re-assessed the PTWI of Cd on the basis of investigations on Cd concentrations in cocoa and related products in 13 countries for the period 2002-2011 [29]. It carried out Cd exposure assessments for cocoa and related products. The results show that the potential dietary Cd exposure in cocoa and related products may be 30-69% PTWI (adult) and up to 96% PTWI in children. Therefore, JECFA set the PTWI for Cd exposure to 2.2-12 μg/kg bw/month for adults and 0.5-12 μg/kg bw/month for children.

2.2 Exposure Analysis

The reference concentrations are based on findings of Chiang et al. and Hsieh et al. Chiang et al. investigated the concentration of heavy-metal background values in commercially available Chinese medicinal preparations, including As, Cd, Pb, Hg, and Cu [30]. They used the standard TCM formula I established by the Taiwan Ministry of Health and Welfare, Committee on Chinese Medicine and Pharmacy, as the priority sampling list. It includes 101 samples from 22 products such as Ban-Long-Wan, Zhigancao-Tang, and Tiaojing-Wan. Each formulation was sampled from three to five Chinese medicine manufacturers with Good Manufacturing Practice (GMP) certification in order to avoid the problem of sampling of manufacturers in a particular region. The sampling must be consistent with the medication and purchasing modes or the general public. Therefore, samples should retain their original packaging to avoid human contamination or the affecting the original condition of the medicine. After sampling, the sample is taken to the laboratory and stored at the temperature of 4℃. Analysis is undertaken as soon as possible. Hsieh et al. conducted an investigation of heavy-metal levels in commercial CHM preparations from Chinese medicine manufacturers, included 154 items from

21 medicine manufacturers. Prescriptions came in soup, powder, and pill form [31]. Medicines included simple prescription and compound prescription, accounting for 61 items and 81 items, respectively. The study identified the concentrations of total arsenic (TAs), Cd, Pb, Hg, and Cu in 43 commonly found CHM preparations, subsequently providing the basis for calculating the human health risk posed by heavy metals in CHM.

Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) is used to detect heavy metals. This is a testing method approved by the Taiwan Food and Drug Administration and is included in the Taiwan Herbal Pharmacopeia. ICP-MS uses high-frequency electromagnetic induction to generate high-temperature argon plasma. After the sample is heated, desolated and decomposed, and atomization or ionization is used for plasma emission spectroscopy, and an optical detector is used to measure the heavy-metal content [32]. ICP-MS detects only the TAs concentration in the sample; however, the harm to humans is due to exposure iAs, which has is more toxic than is As. Therefore, the present study cites the concentrations of TAs and iAs used in 12 types of CHM as tested by Liu et al. to calculate the iAs/TAs ratio [33]. Using this ratio, we estimate the iAs concentration in the CHMs tested by Chiang et al. and Hsieh et al. The dosage forms from Taiwan Herbal Pharmacopeia are recorded in Appendix 1.

The weight parameters are based on the Nutrition and Health Survey in Taiwan, and all ethnic groups aged 18 and above are selected as research subjects [34]. The present study is based on CHM preparations recorded in the Taiwan Herbal Pharmacopeia, with 43 types of CHM preparations divided into nine categories of prescription [32]. For example, category "Kidney" affects the kidneys, category "Blood" affects the blood, and category "Spleen" affects the spleen. A preparation affecting two organs has a category name containing both organs. For example, category "Kidney/Liver" affects the kidney and liver simultaneously. The consumption rate parameters come from the National Health Insurance Research Database in Taiwan by the CHM of nationwide population-based studies. These studies have recorded of the herbal formulas and average daily intake (g/day) in Appendix 2 [35-45]. The average daily intake, concentrations of heavy metals, and weight data are calculated 10,000 times using Crystal Ball® (Version 5.2.2, Decisionerring, Inc., Denver, CO, USA) simulation in order to obtain the best-fitting distribution at 95% confidence interval. If the concentration data has only one value, then Monte Carlo simulation cannot be used; this is marked with "*". In this case, we use a constant value rather than a distribution to calculate risk.

2.3 Risk Characterization

Risk Characterization is an important step in quantifying the risk to determine the adverse health effects of exposure of a group of people to hazardous material in the environment. It can be divided into non-carcinogenic risk characterization and carcinogenic risk characterization. Non-carcinogenic risk is represented by the Hazard Quotient (HQ), while carcinogenic risk is expressed by the Target Risk (TR). HQ is the ratio of the Estimated Daily Intake (EDI) of the contaminant to the HBGV of the hazardous substance. An HQ of less than 1 indicates no potential hazard; an HQ greater than 1 indicates a potential hazard [46]. EDI is the concentration of heavy metals in CHM preparations multiplied by the maximum tolerable consumption rate, divided by body weight. HBGV is developed from the toxicological data collected by international organizations. The present study conducts non-carcinogenic risk characterization of iAs, Cd, Pb, Hg, and Cu, and an additional carcinogenic risk assessment for iAs. The equation is as follows:

$$HQ = \frac{EDI}{HBGV} = \frac{C \times CR}{BW \times HBGV}$$

C: concentration of heavy metal in CHM (mg/kg)
CR: average daily intake of CHM (g/day)
BW: body weight (kg)
HBGV: PTWI, PTMI, PMTDI or the lowest level that causes a critical endpoint (mg/bw kg/day)

TR is used to assess non-threshold risks (such as cancer) and must be calculated using the same exposure pathway [46]. The present study only assesses the carcinogenic risk due to exposure to heavy metals in CHM. In its carcinogenic risk assessment guidelines, the United States Environmental Protection Agency (USEPA) discusses the outcomes of carcinogenic risk. It states that when carcinogenic risk is less than 10^{-6}, then the chance of causing potential harm to humans is negligible; when it is in the range of 10^{-4}-10^{-6}, then the risk is apparent. When it is greater than 10^{-4}, then the risk is unacceptable, and it must be managed to reduce the potential harm. The TR is obtained by multiplying the EDI by the Cancer Slope Factor (CSF). The equation is as follows:

$$TR = EDI \times CSF = \frac{C \times CR \times CSF}{BW}$$

C: concentration of heavy metal in CHM (mg/kg)
CR: average daily intake of CHM (g/day)
BW: body weight (kg)
CSF: cancer slope factor $(mg/kg\ bw/day)^{-1}$

III. Result

3.1 Exposure Assessment

Liu et al. tested the concentration of AsIII, AsV, and TAs in 12 types of CHM [33]. The iAs/TAs conversion ratio is 0.83 (Table no 1). This study multiplies the concentration of TAs obtained by Chiang et al. and Hsieh et al. by this ratio in order to obtain the iAs concentration [30,31].

Table no 1: The transformation ratio between inorganic arsenic (iAs) and total arsenic (TAs) in Traditional Chinese Medicines.

Chinese herbal medicine	Concentration[a] (mean±SD) (ng/g)			iAs ratio
	As^{III}	As^{V}	TAs	
I. indigotica (板藍根)	120.20	1.10	137.40	0.88
A. macrocephala (白朮)	181.80	61.30	371.90	0.65
S. miltiorrhiza (丹蔘)	84.00	52.00	278.90	0.49
S. divaricata (防風)	47.20	108.30	175.80	0.88
A. membranaceus (黃耆)	66.80	39.80	140.30	0.76
A. tataricus (紫菀)	91.40	264.10	525.50	0.68
A. asphodeloides (知母)	23.90	105.80	216.20	0.60
T. kirilowii (栝樓根)	79.90	52.60	184.40	0.72
S. tenuifolia (荊芥)	187.30	168.80	259.20	1.37
I. indigotica (板藍芽)	116.70	60.80	195.20	0.91
T. kirilowii (栝樓芽)	25.50	37.20	39.10	1.60
D. morifolium (藥菊)	110.20	303.60	351.40	1.18
Total	1134.90	1255.40	2875.30	0.83

[a]Liu et al. (2013)

We categorize 43 common types of CHM into 9 categories of prescriptions: Blood (B), Blood/Painkiller (BP), Diaphoretic/Heat Cleaning (D), Kidney (K), Kidney/Liver (KL), Liver (L), Liver/Spleen (LS), Lung (Lu), And Stomach/Spleen (S). The concentrations of heavy metals are iAs, Cd, Cu, Pb, and Hg, respectively. The Hg concentrations in the prescription B and LS, as well as Cu concentrations in the prescription BP and L, are constant: 0.01, 0.01, 5.62 and 3.07. The remaining heavy metals and prescriptions have geometric means and geometric standard deviations (Table no 2). The best-fitting distribution is a lognormal distribution. The average daily intake for the 9 types of prescription are 5.16 (B), 5.28 (BP), 4.01 (D), 4.79 (K), 5.17 (KL), 1.65 (L), 4.16 (LS), 3.23 (Lu) and 3.05 (S). The research subjects are all ethnic individuals aged 18 and above, screened by weight. There were 3,042 respondents with an average weight of 63.78 kg. The best-fitting distribution is a normal distribution (Table no 3).

Table no 2: Heavy metal levels of Traditional Chinese Medicines prescription.

Prescription Effect	Formula Name	Concentration (mg/kg)				
		iAs	Cd	Pb	Hg	Cu
Blood	Ban-Long Wan (斑龍丸)[a]	LN(0.32,1.39)[c]	LN(0.07,2.03)	LN(0.57,2.02)	0.01[d]	LN(2.19,1.34)
	Shu-Jing-Huo-Xue Tang (疏經活血湯)[b]					

	Zhigancao Tang (炙甘草湯)[b]					
Blood/Painkiller	Tiaojing Wang (調經丸)[a]	LN(0.34,1.54)	LN(0.16,1.48)	LN(2.10,1.51)	LN(3.13,2.09)	5.62[d]
	Xuefu-Zhuyu Tang (血府逐瘀湯)[b]					
	Chuan-Xiong-Cha-Tiao San (川芎茶調散)[a]					
	Shang-Zhong-Xia-Tong-Yong-Tong-Feng Wan (上中下通用痛風丸)[a]					
Diaphoretic/Heat-cleaning	Huang-Lian-Jie-Du Tang (黃連解毒湯)[b]	LN(0.21,1.55)	LN(0.07,2.34)	LN(0.64,1.91)	LN(0.02,3.06)	LN(1.74,3.56)
	Gan-Lu Yin (甘露飲)[b]					
	Xiao-Feng San (消風散)[b]					
	Hsiao-Chih Wan (消痣丸)[a]					
	Qingxin-Lianzi Tang (清心蓮子湯)[b]					
	Chai-Ge-Jie-Ji Tang 柴葛解肌湯)[b]					
	Gui-Zhi Tang (桂枝湯)[b]					
	Xiao-Qing-Long Tang (小青龍湯)[b]					
	Ge-Gen Tang (葛根湯)[b]					
	Huo-Xiang-Zheng-Qi San (藿香正氣散)[b]					
	Fangfeng-Tōng-Sheng San (防風通聖散)[b]					
	Ching-Fang-Pai-Tu Tang (荊防敗毒湯)[b]					
Kidney	Sang-Piao-Xiao San (桑螵蛸散)[a]	LN(0.34,2.22)	LN(0.05,3.76)	LN(0.87,2.26)	LN(0.02,4.24)	LN(2.94,1.39)
	Liu-Wei-Di-Huang Wan (六味地黃丸)[b]					
	Ba-Wei-Di-Huang Wan (八味地黃丸)[b]					
	Ji-Sheng-Shen-Qi Wan (濟生腎氣丸)[b]					
Kidney/Liver	Huan-Shao Dan (還少丹)[a]	LN(0.20,1.36)	LN(0.04,1.34)	LN(0.60,1.74)	LN(0.02,2.65)	LN(2.17,1.09)
	Qi-Ju-Di-Huang Wan (杞菊地黃丸)[b]					
	Zhi-Bai-Di-Huang Wan (知柏地黃丸)[b]					
	Du-Huo-Ji-Sheng Tang (獨活寄生湯)[b]					
Liver	Yang-Gan Wang (養肝丸)[a]	LN(0.24,1.24)	LN(0.07,1.63)	LN(0.63,1.66)	LN(0.02,2.17)	3.07[d]
	Long-Dan-Xie-Gan Tang (龍膽瀉肝湯)[b]					
Liver/Spleen	Si-Ni San (四逆散)[b]	LN(0.18,1.17)	LN(0.04,2.12)	LN(0.03,1.48)	0.01[d]	LN(2.89,1.65)
	Xiao-Yao San (逍遙散)[b]					
	Jia-Wei-Xiao-Yao San (加味逍遙散)[b]					
Lung	Hua-Gai San (華蓋散)[b]	LN(0.23,1.81)	LN(0.06,2.99)	LN(0.65,2.46)	LN(0.01,1.49)	LN(2.31,1.36)
	Er-Chen Tang (二陳湯)[b]					

	Ning-Sou Wang (寧嗽丸)[a]					
	Qing-Fei Tang (清肺湯)[b]					
	Zhi-Sou San (止嗽散)[b]					
	Xin-Yi-Qing-Fei Tang (辛夷清肺湯)[b]					
	Ma-Xing-Gan-Shi-Tang (麻杏甘石湯)[b]					
Stomach/Spleen	Xiang-Sha-Liu-Jun-Zi Tang (香砂六君子湯)[b]	LN(0.13,1.81)	LN(0.05,2.02)	LN(0.53,1.47)	LN(0.02,2.50)	LN(3.17,1.42)
	Liu-Jun-Zi Tang (六君子湯)[b]					
	Shen-Lin-Bai-Zhu San (蔘苓白朮散)[a]					
	Bu-Zhong-Yi-Qi Tang (補中益氣湯)[b]					

[a] Chiang et al. (2002).
[b] Hsieh et al. (2013).
[c] Lognormal distribution (mean, geometric standard deviation).
[d] A single value obtained from Chiang et al. (2002) or Hsieh et al. (2013) can't be analyzed by Crystal Ball software.

3.2 Dose-Response Analysis

A study on the dose responses of iAs by JECFA in 2011 analyzed the results of three new epidemiological studies [14]. It found that the PTWI (0.015 mg/kg bw/day) was no longer health protective. Therefore, the PTWI was revoked, as the standard for assessing risk. The BMDL0.5 of iAs is 0.003 mg/kg bw/day for lung cancer [15], 0.0052 mg/kg bw/day for bladder cancer [16] and 0.0054 mg/kg bw/day for skin lesions [17]. In 1988, the Integrated Risk Information System (IRIS) of the USEPA set the oral Reference Dose (RfD) as 0.0003 mg/kg bw/day with the endpoint was hyperpigmentation, keratosis and possible vascular complications [47]. We also used CSF for iAs to 1.5(mg/kg bw/day)$^{-1}$for skin cancer (Table no 4).

The HBGV for Pb is a point of departure, 0.0012 mg/kg bw/day, which is the Pb exposure level that produces a 1 mm Hg increase in SBP of adults [14]. The PTWI for Hg is 0.004 mg/bw kg/weekly. Exposure of rats to Hg resulted in an increase in renal Hg concentration and changes in kidney weight. The rat exposure dose was then extrapolated to the dose for humans [24]. The PMTDI of Cu is 0.5 mg/bw kg/weekly, which is based on the JECFA requirement of 2-3 mg/day of Cu for adults [26]. Experiments on dogs confirm no cumulative toxicological effects on humans [25]. According to JECFA in 2013, the PTWI for Cd is 0.025 mg/bw kg/weekly, on the basis of the potential exposure to Cd in cocoa and related products (36-69% PTMI in adults, 96% PTMI in children [29] (Table no 3).

3.3 Risk Assessment

The present study uses HQ to calculate non-carcinogenic risk and TR to assess carcinogenic risk. Data are shown using the median figures (P5-P95). Because of the critical endpoints caused by iAs include bladder cancer and lung cancer are used BMDL, we compared to EDI and BMDL rather than EDI divided by BMDL. The highest EDI of bladder cancer and lung cancer are 2.85×10^{-5} and 2.84×10^{-5} with prescription BP, the lowest EDI of bladder cancer and lung cancer are 6.29×10^{-6} and 6.22×10^{-6} with prescription L. There are all lower than BMDL of bladder cancer (0.0052 mg/kg bw/day) and lung cancer (0.003 mg/kg bw/day). If we used CSF to assess skin cancer by exposure iAs, the highest TR is 4.25×10^{-5} with prescription BP, the lowest TR is 9.36×10^{-6} with prescription L. All prescriptions are in the acceptable range (10^{-4}-10^{-6}). In the non-carcinogenic risk, the critical endpoint of iAs is skin lesion. The prescription with the highest HQ is the BP prescription, with values of 5.25×10^{-3}, the prescription with the lowest HQ is the LS prescription, with values of 1.15×10^{-4}, respectively(Fig. no1).

Table no 3: Variables used in Pb, Hg, Cu and Cd probabilistic risk assessment

Parameter	**Factor**	**Reference**
Average daily intake (g/day)		
Blood	LN(5.16,1.38)	See Appendix 2

Blood/Painkiller	LN(5.28,1.21)	
Diaphoretic/Heat-cleaning	LN(4.01,1.18)	
Kidney	LN(4.79,1.25)	
Kidney/Liver	LN(5.17,1.53)	
Liver	1.65[a]	
Liver/Spleen	LN(4.16,1.38)[b]	
Lung	LN(3.23,1.32)	
Stomach/Spleen	LN(3.05,1.47)	
Body Weight (kg)		
Whole group	N(63.78,10.75)[c]	NAHSIT[d] (2005-2008, 2010, 2011, 2012)
Point of departure (mg/kg bw/day)		
Pb (for 1 mmHg increase in blood pressure in adults)	0.0012	JECFA[e] (2011)
Provisional tolerable weekly intake (mg/bw kg/weekly)		
Hg	0.004	JECFA (2011)
Provisional maximum tolerable daily intake (mg/bw kg/day)		
Cu	0.5	JECFA (1982)
Provisional tolerable monthly intake (mg/kg bw/monthly)		
Cd	0.025	JECFA (2013)

[a]A single value obtained from paper can't be analyzed by Crystal Ball software.
[b] Lognormal distribution (mean, standard deviation).
[c] Normal distribution (mean, standard deviation).
[d] Nutrition and Health Survey in Taiwan.
[e] The Joint FAO/WHO Expert Committee on Food Additives.

Table no 4: Parameters used in iAs probabilistic risk assessment

Parameter	Factor	Reference
The benchmark dose for a 0.5% increased incidence (mg/kg bw/day)		
iAs (lung cancer)	0.003	JECFA[a] (2011)
iAs (bladder cancer)	0.0052	JECFA[a] (2011)
iAs (skin lesions)	0.0054	JECFA[a] (2011)
Oral Reference Dose (mg/kg bw/day)		
iAs (Hyperpigmentation, keratosis and possible vascular complications)	0.0003	IRIS[b] (1988)
Cancer Slope Factor $(mg/kg\ bw/day)^{-1}$		
iAs (skin cancer)	1.5	IRIS(1988)

[a]The Joint FAO/WHO Expert Committee on Food Additives.
[b] Integrated Risk Information System from United States Environmental Protection Agency.

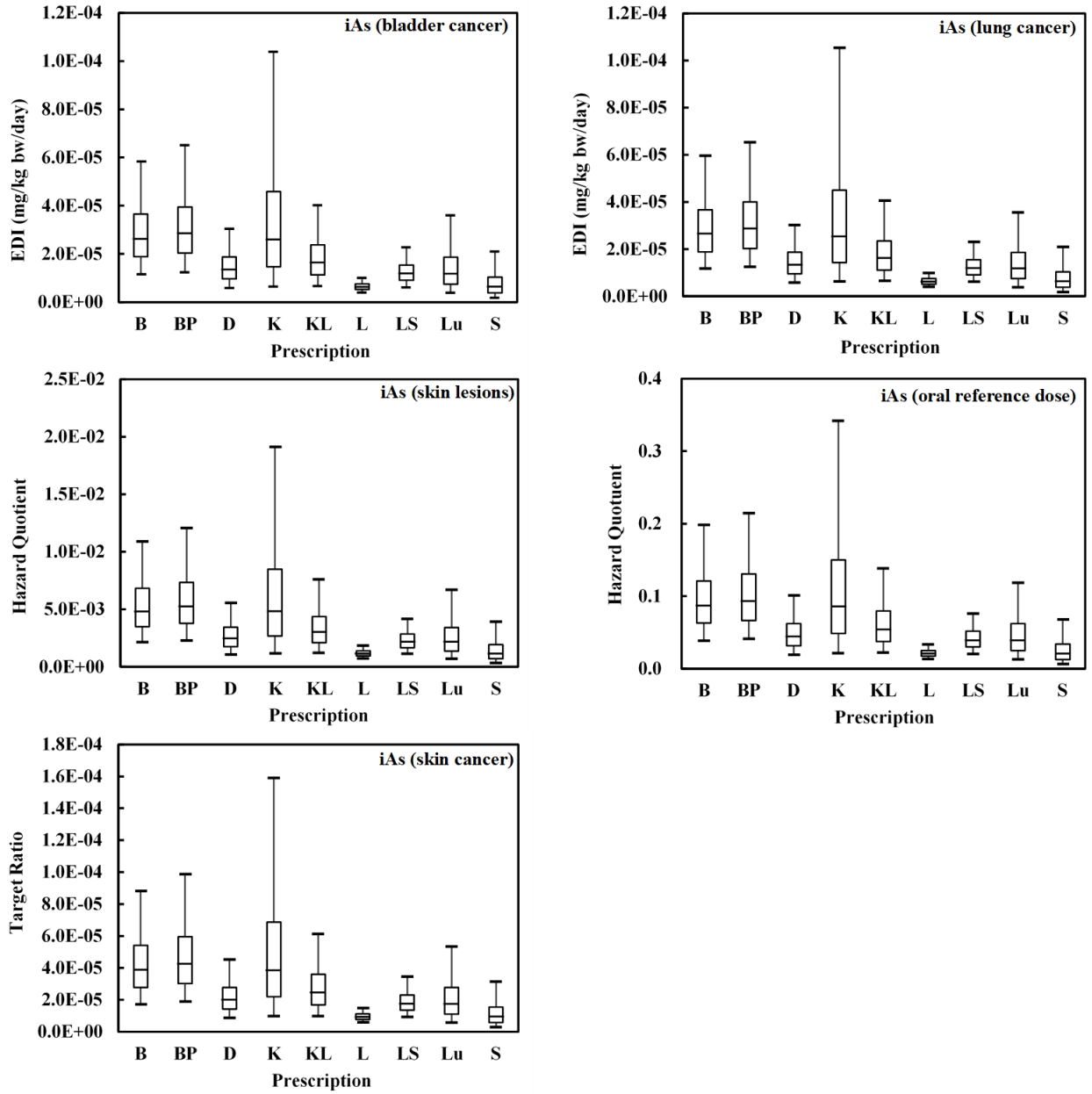

Fig. no 1: The carcinogenic and non-carcinogenic risk of iAs in whole group. Bladder cancer and lung cancer are estimated daily intake (EDI) compared to BMDL0.5 (bladder cancer: 0.003 mg/kg bw/day; lung cancer: 0.0052 mg/kg bw/day). Skin cancer is assessed carcinogenic risk by target cancer risk. Non-carcinogenic risk is assessed by hazard quotient (HQ) by used BMDL0.5 and oral reference dose (RfD). Q1: 5%, Q2: 25%, Median: 50%, Q3: 75% and Q4: 95%. Prescription abbreviation: B (blood); BP (blood and painkiller); D (diaphoretic and heat-cleaning); K (kidney); KL (kidney and liver); L (liver); LS (liver and spleen); Lu (lung) and S (stomach and spleen).

In the coming paragraph, the non-carcinogenic risk of other metals including Cd, Cu, Hg and Pb will be described. All HQs are lower than 1, mean the non-carcinogenic risk is acceptable. The highest HQ of Cd, Cu, Hg and Pb is the prescription BP, with a value of 1.60×10^{-2}, 9.37×10^{-4}, 4.61×10^{-1} and 1.46×10^{-1}. The lowest HQ of Cd, Cu, Hg and Pb is the prescription L, Lu and LS, with a value of 2.19×10^{-3}, 1.60×10^{-4}, 8.87×10^{-4} and 1.64×10^{-3}(Fig. no 2).

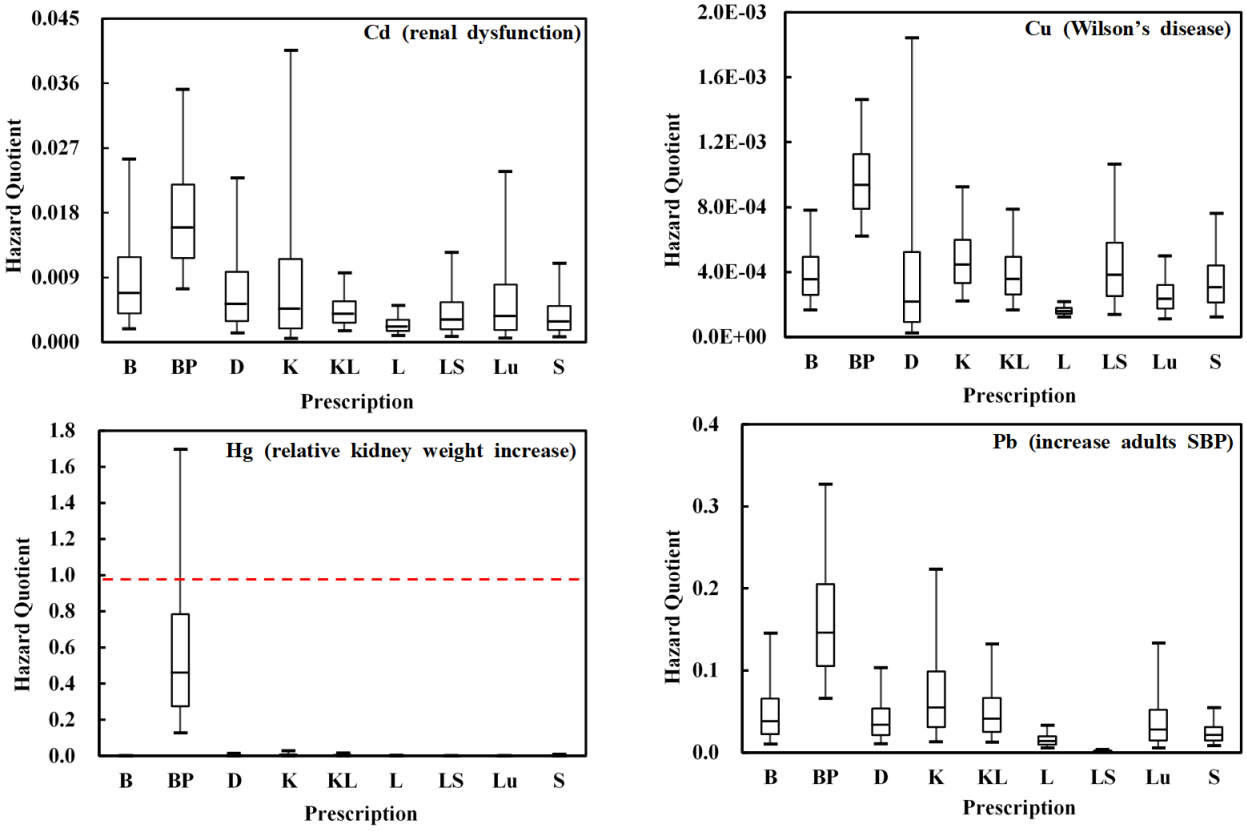

Fig. no 2: Estimated hazard quotient (HQ) of Cd, Cu, Hg and Pb in whole group. Q1: 5%, Q2: 25%, Median: 50%, Q3: 75% and Q4: 95%. Prescription abbreviation: B (blood); BP (blood and painkiller); D (diaphoretic and heat-cleaning); K (kidney); KL (kidney and liver); L (liver); LS (liver and spleen); Lu (lung) and S (stomach and spleen). SBP: systolic blood pressure.

3.4 Uncertainty Analysis

The present study uses HBGV as a tool to quantify risks. Animal experiments or epidemiological investigations extrapolated to humans may produce interspecies or intraspecies differences. Data from animal experiments extrapolated to humans may overestimate risk, and epidemiological investigations may ignore specific or sensitive groups, causing an underestimation of risk. Concentration data come from analysis of different samples of CHM. The types of CHM gathered do not entirely match the usage habits of ordinary people, causing a possible underestimation of risk. Obtaining the consumption rate data from other studies, using average daily intake rather than actual doses of CHM, possibly overestimates or underestimates risk.

3.5 Implications

Heavy metals in CHM are primarily derived from the soil and water during cultivation, and they may be used in fertilizers or as a source of nutrition. The bioavailability and toxicological effects of heavy metals on the ecosystem may affect the heavy-metal content of CHMs. In addition, CHMs absorb minerals and nutrition sources from the natural environment during growth [48]. The site of CHM cultivation also has a large effect on the heavy-metal content. Ramirez-Andreotta et al. investigated the arsenic concentration of non-medicinal plants and found that plants grown near mines and smelting plants have high heavy-metal content [49]. Annan et al. sampled 10 types of medicinal plants from 5 different sites and analyzes the heavy-metal concentration of 5 types of plants [50]. They found that plants grown in different environments accumulate different concentrations of heavy metals. The safety of CHM cultivation can be ensured by good agricultural practice (GAP) and GMP, which can reduce the concentrations of heavy metals from the environment absorbed by medicinal plants and thus control the risk.

The heavy-metal content of CHMs may be the result of cross-contamination during processing, including drying, grinding, and extraction [51]. Methods of extracting CHM may increase heavy-metal concentrations; for example, continuous boiling CHMs in water produces higher concentrations of heavy metals as compared with simply soaking the CHM in hot water [52]. Some CHMs may also have added salts containing heavy metals during preparation. Because of traditional use, these additions are believed to increase the

effectiveness of CHM; this may result in increased concentrations of heavy metals [53]. The safety of CHM processing can be improved by reducing the drying rate of CHM or by increasing the proportion of water. Soaking rather than boiling when preparing CHM can also reduce the concentration of heavy metals. Finally, care should be taken to see whether additional heavy metals have been added when choosing a CHM in order to ensure that the potential risk from excessive intake of heavy metals is not greater than the medicinal effects.

IV. Conclusion

In conclusion, the non-carcinogenic risk posed by iAs, Cd, Cu, Hg and Pb are within the acceptable safety range for human health, and the carcinogenic risk posed by iAs is also acceptable. Only the P95 with prescription BP of Hg is higher than 1, with a value of 1.7. The safety of CHM can be improved by GAP and GMP, and by reducing the heavy-metal levels in the environment as possible. Further study can focus on vulnerable groups such as the elderly, children, pregnant, or high-risk groups (patients using CHM in the long term). Although the results of this study show excessive heavy-metal concentrations in nine prescription types (B, BP, G, K, KL, L, LS, Lu, and S), most people only take a single prescription when taking Chinese medicine. There are few cases of using more than one prescription at the same time. Therefore, the consumption rate used in this study is conservatively based on the daily maximum dose in a prescription. which means that there may be risk of overestimation. On the basis of the above discussion, when can expect that the risk of harm posed by heavy-metal (iAs, Pb, Hg, Cu, and Cd) exposure to Taiwanese taking prescription medicine is within an acceptable range.

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Appendix

Appendix no 1: The content of Traditional Chinese Medicines prescription

Prescription Effect	**Formula Name**	**Ingredients (g)**	**Type**
Blood	Ban-Long Wan (斑龍丸)[a]	Cornu Cervi Degelatinatum (5.0), Deerhorn Glue (5.0), Chinese Dodder Seed (5.0), Chinese Arborvilae Seed (5.0), Processed Rehmannia Root (5.0), Indian Buead Tuckahoe (2.5), Malaytea Scurfpea Fruit (2.5)	Soup

	Shu-Jing-Huo-Xue Tang (疏經活血湯)[b]	Liquorice Root (1.0), Chinese Angelica (2.0), White Peony Root (2.5), Adhesive Rehmannia Root Tuber (2.0), Swordlike Atracylodes Rhizome (2.0), Common Achyranthes (2.0), Tangerine Peel (2.0), Peach Seed (2.0), Chinese Clematis (2.0), Szechwan Lovage Rhizome (1.0), Fourstamen Stephania Root (1.0), Incised Notopterygium Rhizome And Root (1.0), Divaricate Saposhnikovia (1.0), Taiwan Angelica Root (1.0), Longdan (1.0), Indian Buead Tuckahoe (1.0), Fresh Ginger (3.0)	Pill
	Zhigancao Tang (炙甘草湯)[b]	Honey-Fried Licorice Root (3.0), Fresh Ginger (2.5), Cassiabarktree Twig (2.5), Panax Ginseng (1.5), Adhesive Rehmannia Root Tuber (12.0), Ass-Hide Gelatin (1.5), Creeping Liriope (2.5), Hemp Fruit (3.0), Common Jujube (3.0)	Soup
Blood/Painkiller	Tiaojing Wang (調經丸)[a]	Nutgrass Galingale Rhizome (4.0), Eucommia Bark (4.0), Szechwan Lovage Rhizome (2.0), White Peony Root (2.0), Chinese Angelica (2.0), Adhesive Rehmannia Root Tuber (2.0), Tangerine Peel (2.0), Fennel Fruit (2.0), Corydalis Yanhusuo (2.0), Desertliving Cistanche Herb (2.0), Immature Tangerine Fruit (2.0), Combined Spicebush Root (2.0), Baikal Skullcap Root (2.0), Cuttlebone Sepium (2.0)	Pill
	Xuefu-Zhuyu Tang (血府逐瘀湯)[b]	Chinese Angelica (4.5), Adhesive Rehmannia Root Tuber (4.5), Peach Seed (6.0), Safflower (4.5), Submature Bitter Orange (3.0), Red Paeoniae Trichocarpae (3.0), Chinese Thorawax Root (1.5), Liquorice Root (1.5), Balloonflower Root (2.3), Szechwan Lovage Rhizome (2.3), Common Achyranthes (4.5)	Soup
	Chuan-Xiong-Cha-Tiao San (川芎茶調散)[a]	Taiwan Angelica Root (2.0), Liquorice Root (2.0), Incised Notopterygium Rhizome And Root (2.0), Fineleaf Schizonepeta Herb (4.0), Szechwan Lovage Rhizome (4.0), Manchurian Wildginger Herb (1.0), Divaricate Saposhnikovia (1.5), Wild Mint Herb (8.0)	Powder
	Shang-Zhong-Xia-Tong-Yong-Tong-Feng Wan (上中下通用痛風丸)[a]	Arisaema Heterophyllum (4.0), Swordlike Atracylodes Rhizome (4.0), Amur Corktree Bark (4.0), Szechwan Lovage Rhizome (2.0), Taiwan Angelica Root (2.0), Massa Medicata Fermentata (2.0), Peach Seed (2.0), Chinese Clematis (1.0), Incised Notopterygium Rhizome And Root (1.0), Fourstamen Stephania Root (2.0), Cassiabarktree Twig (1.0), Safflower (0.5), Longdan (2.0)	Pill
Diaphoretic/ Heat-cleaning	Huang-Lian-Jie-Du Tang (黃連解毒湯)[b]	Coptis Chinensis (6.0), Baikal Skullcap Root (6.0), Amur Corktree Bark (6.0), Common Gardenia Fruit (6.0)	Soup
	Gan-Lu Yin (甘露飲)[b]	Processed Rehmannia Root (2.5), Creeping Liriope (2.5), Submature Bitter Orange (2.5), Honey-Fried Licorice Root (2.5), Artemisia Capillaris (2.5), Loquat Leaves (2.5), Dendrobium Nobile (2.5), Baikal Skullcap Root (2.5), Adhesive Rehmannia Root Tuber (2.5), Asparagus Cochinchinensis (2.5)	Soup
	Xiao-Feng San (消風散)[b]	Chinese Angelica (2.5), Adhesive Rehmannia Root Tuber (2.5), Divaricate Saposhnikovia (2.5), Cicada Slough (2.5), Common Anemarrhena (2.5), Kushen (2.5), Flax (2.5), Fineleaf Schizonepeta Herb (2.5), Swordlike Atracylodes Rhizome (2.5), Great Burdock Fruit (2.5), Gypsum (2.5), Liquorice Root (1.25), Akabia Stem (1.25)	Powder
	Hsiao-Chih Wan (消痣丸)[a]	Adhesive Rehmannia Root Tuber (4.8), Baikal Skullcap Root (1.8), Lonicera Japonica (1.2), Submature Bitter Orange (1.2), Largeleaf Gentian Root (1.2), Divaricate Saposhnikovia (2.4), Rhubarb Tangute Rhubarb (2.4), Chinese Angelica (2.4), Swordlike Atracylodes Rhizome (2.4), Dilong (2.4), Black Locust Flower (2.4), Red Paeoniae Trichocarpae (2.4)	Pill
	Qingxin-Lianzi Tang (清心蓮子湯)[b]	Lotus Seed (4.5), Indian Buead Tuckahoe (4.5), Astragalus Membranaceus (4.5), Panax Ginseng (4.5), Creeping Liriope (3.0), Chinese Wolfberry Root-Bark (3.0), Baikal Skullcap Root (3.0), Honey-Fried Licorice Root (3.0), Plantago Asiatica (3.0)	Soup
	Chai-Ge-Jie-Ji Tang 柴葛解肌湯)[b]	Chinese Thorawax Root (2.5), Lobed Kudzuvine Root (2.5), Incised Notopterygium Rhizome And Root (2.5), Taiwan Angelica Root (2.5), Baikal Skullcap Root (2.5), White Peony Root (2.5), Balloonflower Root (2.5), Liquorice Root (1.5), Gypsum (2.5), Fresh Ginger (2.0), Common Jujube (2.0)	Soup
	Gui-Zhi Tang (桂枝湯)[b]	Cassiabarktree Twig (3.0), Baikal Skullcap Root (3.0), Panax Ginseng (3.0), Honey-Fried Licorice Root (2.0), Ternate Pinellia (5.0), White Peony Root (3.0), Common Jujube (2.0), Fresh Ginger (3.0), Chinese Thorawax Root (8.0)	Soup
	Xiao-Qing-Long Tang (小青龍湯)[b]	Chinese Ephedrs Herb (4.0), White Peony Root (4.0), Chinese Magnoliavine Fruit (1.5), Dried Ginger (4.0), Honey-Fried Licorice Root (4.0), Cassiabarktree Twig (4.0), Ternate Pinellia (4.0), Manchurian Wildginger Herb (1.5)	Soup
	Ge-Gen Tang (葛根湯)[b]	Lobed Kudzuvine Root (6.0), Chinese Ephedrs Herb (4.5), Cassiabarktree Twig (3.0), White Peony Root (3.0), Honey-Fried Licorice Root (3.0), Fresh Ginger (4.5), Common Jujube (4.0)	Soup
	Huo-Xiang-Zheng-Qi San (藿香正氣散)[b]	Areca Peel (3.0), Indian Buead Tuckahoe (3.0), Taiwan Angelica Root (3.0), Perilla Frutescens (3.0), Tangerine Peel (2.0), Balloonflower Root (2.0), Atractylodes Rhizome (2.0), Officinal Magnolia Bark (2.0), Ternate Pinellia (2.0), Honey-Fried Licorice Root (1.0), Pogostemon Cablin (3.0), Fresh Ginger (3.0), Common Jujube (1.0)	Pill
	Fangfeng-Tōng-Sheng San (防風通聖散)[b]	Divaricate Saposhnikovia (1.0), Fineleaf Schizonepeta Herb (1.0), Forsythia (1.0), Chinese Ephedrs Herb (1.0), Wild Mint Herb (1.0), Szechwan Lovage Rhizome (1.0), Chinese Angelica (1.0), White Peony Root (1.0), Atractylodes Rhizome (1.0), Common Gardenia Fruit (1.0), Rhubarb Tangute Rhubarb (1.0), Mirabilite Glauber's Salt (1.0), Baikal Skullcap Root (2.0), Gypsum (2.0), Balloonflower Root (2.0), Liquorice Root (4.0), Huashi (6.0), Fresh Ginger (2.0), Fistular Onion Stalk (2.0)	Powder

	Ching-Fang-Pai-Tu Tang (荊防敗毒湯)[b]	Fineleaf Schizonepeta Herb (3.0), Divaricate Saposhnikovia (3.0), Incised Notopterygium Rhizome And Root (3.0), Doubleteeth Angelicae Root (3.0), Chinese Thorawax Root (3.0), Whiteflower Hogfennel Root Common Hogfennel Root (3.0), Szechwan Lovage Rhizome (3.0), Submature Bitter Orange (3.0), Balloonflower Root (3.0), Indian Buead Tuckahoe (3.0), Liquorice Root (1.5), Fresh Ginger (3.0), Wild Mint Herb (1.0)	Soup
Kidney	Sang-Piao-Xiao San (桑螵蛸散)[a]	Mantis Egg-Case (3.0), Thinleaf Milkwort Willd (3.0), Acorus Calamus (3.0), Longgu (3.0), Panax Ginseng (3.0), Indian Buead Tuckahoe (3.0), Chinese Angelica (3.0), Tortoiseshell (3.0)	Powder
	Liu-Wei-Di-Huang Wan (六味地黃丸)[b]	Processed Rehmannia Root (8.0), Common Macrocarpium Fruit (4.0), Common Yan Rhizome (4.0), Oriental Waterplantain Tuber (3.0), Mudanpi (3.0), Indian Buead Tuckahoe (3.0)	Pill
	Ba-Wei-Di-Huang Wan (八味地黃丸)[b]	Indian Buead Tuckahoe (3.0), Mudanpi (3.0), Oriental Waterplantain Tuber (3.0), Processed Rehmannia Root (8.0), Common Macrocarpium Fruit (4.0), Common Yan Rhizome (4.0), Radix Aconiti Praeparata (1.0), Cassia Bark (1.0)	Pill
	Ji-Sheng-Shen-Qi Wan (濟生腎氣丸)[b]	Processed Rehmannia Root (8.0), Common Macrocarpium Fruit (4.0), Common Yan Rhizome (4.0), Indian Buead Tuckahoe (6.0), Mudanpi (3.0), Oriental Waterplantain Tuber (3.0), Radix Aconiti Praeparata (1.0), Cassia Bark (1.0), Common Achyranthes(2.0), Plantago Asiatica (2.0)	Pill
Kidney/Liver	Huan-Shao Dan (還少丹)[a]	Common Yan Rhizome (3.0), Common Achyranthes (3.0), Indian Buead Tuckahoe (2.0), Common Macrocarpium Fruit (2.0), Chushi (2.0), Eucommia Bark (2.0), Chinese Magnoliavine Fruit (2.0), Morinda Officinalis (2.0), Desertliving Cistanche Herb (2.0), Thinleaf Milkwort Willd (2.0), Fennel Fruit (2.0), Acorus Gramineus (1.0), Processed Rehmannia Root (1.0), Babury Wolfberry Fruit (1.0), Common Jujube (1.0)	Pill
	Qi-Ju-Di-Huang Wan (杞菊地黃丸)[b]	Babury Wolfberry Fruit (2.0), Camomile (2.0), Processed Rehmannia Root (8.0), Common Macrocarpium Fruit (4.0), Common Yan Rhizome (4.0), Indian Buead Tuckahoe (3.0), Mudanpi (3.0), Oriental Waterplantain Tuber (3.0)	Pill
	Zhi-Bai-Di-Huang Wan (知柏地黃丸)[b]	Processed Rehmannia Root (8.0), Common Macrocarpium Fruit (4.0), Indian Buead Tuckahoe (3.0), Common Yan Rhizome (4.0), Mudanpi (3.0), Oriental Waterplantain Tuber (3.0), Common Anemarrhena (2.0), Amur Corktree Bark (2.0)	Pill
	Du-Huo-Ji-Sheng Tang (獨活寄生湯)[b]	Doubleteeth Angelicae Root (3.0), Taxillus Chinensis (2.0), Eucommia Bark (2.0), Common Achyranthes (2.0), Manchurian Wildginger Herb (2.0), Largeleaf Gentian Root (2.0), Indian Buead Tuckahoe (2.0), Guixin (2.0), Divaricate Saposhnikovia (2.0), Szechwan Lovage Rhizome (2.0), Panax Ginseng (2.0), Liquorice Root (2.0), Chinese Angelica (2.0), White Peony Root (2.0), Adhesive Rehmannia Root Tuber (2.0)	Soup
Liver	Yang-Gan Wang (養肝丸)[a]	Chinese Angelica (3.5), Plantago Asiatica (3.5), White Peony Root (3.5), Divaricate Saposhnikovia (3.5), Ruiren (3.5), Processed Rehmannia Root (3.5), Szechwan Lovage Rhizome (3.5), Papermulberry Fruit (3.5)	Pill
	Long-Dan-Xie-Gan Tang (龍膽瀉肝湯)[b]	Longdan (4.0), Baikal Skullcap Root (2.0), Common Gardenia Fruit (2.0), Oriental Waterplantain Tuber (4.0), Akabia Stem (2.0), Plantago Asiatica (2.0), Chinese Angelica (2.0), Adhesive Rehmannia Root Tuber (2.0), Chinese Thorawax Root (4.0), Liquorice Root (2.0)	Pill
Liver/Spleen	Si-Ni San (四逆散)[b]	Liquorice Root (6.0), Immature Bitter Orange (6.0), Chinese Thorawax Root (6.0), White Peony Root (6.0)	Powder
	Xiao-Yao San (逍遙散)[b]	Honey-Fried Licorice Root (2.0), White Peony Root (4.0), Chinese Angelica (4.0), Indian Buead Tuckahoe (4.0), Atractylodes Rhizome (4.0), Chinese Thorawax Root (4.0), Roast Ginger (4.0), Wild Mint Herb (2.0)	Powder
	Jia-Wei-Xiao-Yao San (加味逍遙散)[b]	Chinese Angelica (4.0), Atractylodes Rhizome (4.0), White Peony Root (4.0), Chinese Thorawax Root (4.0), Indian Buead Tuckahoe (4.0), Honey-Fried Licorice Root (2.0), Mudanpi (2.5), Common Gardenia Fruit (2.5), Roast Ginger (4.0), Wild Mint Herb (2.0)	Powder
Lung	Hua-Gai San (華蓋散)[b]	Chinese Ephedrs Herb (4.0), Suzi (4.0), Sangbaipi (4.0), Apricot Kernel (4.0), Red Glacier (4.0), Tangerine Peel (4.0), Liquorice Root (2.0)	Powder
	Er-Chen Tang (二陳湯)[b]	Ternate Pinellia (8.0), Tangerine Peel (8.0), Indian Buead Tuckahoe (5.0), Honey-Fried Licorice Root (2.5), Fresh Ginger (2.5)	Pill
	Ning-Sou Wang (寧嗽丸)[a]	Balloonflower Root (3.0), Dendrobium (3.0), Ternate Pinellia (3.0), Tendrilleaf Fritillary Bulb (3.0), Suzi (3.0), Indian Buead Tuckahoe (3.0), Wild Mint Herb (2.3), Apricot Kernel (2.3), Sangbaipi (2.3), Exocarpium Citri Rubrum (1.5), Rice-Grain Sprout (1.5), Liquorice Root (0.8)	Pill
	Qing-Fei Tang (清肺湯)[b]	Liquorice Root (0.6), Baikal Skullcap Root (3.0), Balloonflower Root (2.0), Indian Buead Tuckahoe (2.0), Tangerine Peel (2.0), Chinese Angelica (2.0), Tendrilleaf Fritillary Bulb (2.0), Sangbaipi (2.0), Asparagus Cochinchinensis (1.5), Common Gardenia Fruit (1.5), Apricot Kernel (1.5), Creeping Liriope (1.5), Chinese Magnoliavine Fruit (0.4), Fresh Ginger (3.0), Common Jujube (2.0), Bamboo Shavings (2.0)	Soup
	Zhi-Sou San (止嗽散)[b]	Balloonflower Root (5.0), Fineleaf Schizonepeta Herb (5.0), Aster Tataricus (5.0), Japanese Stemona Root (5.0), Willowleaf Swallowwort Rhizome And Root (5.0), Liquorice Root (2.0), Tangerine Peel (2.5)	Powder
	Xin-Yi-Qing-Fei Tang (辛夷清肺湯)[b]	Biod Magnolia Bud (2.0), Baikal Skullcap Root (3.0), Common Gardenia Fruit (3.0), Creeping Liriope (3.0), Greenish Lily Bulb (3.0), Gypsum (3.0), Common	Soup

		Anemarrhena(3), Liquorice Root (1.5), Loquat Leaves (3.0), Skunk Bugbane Rhizome (1.0)	
	Ma-Xing-Shi-Gan Tang (麻杏甘石湯)[b]	Chinese Ephedrs Herb (8.0), Apricot Kernel (6.0), Honey-Fried Licorice Root (4.0), Gypsum (16.0)	Soup
Stomach/Spleen	Xiang-Sha-Liu-Jun-Zi Tang (香砂六君子湯)[b]	Panax Ginseng (2.5), Atractylodes Rhizome (5.0), Indian Buead Tuckahoe (5.0), Liquorice Root (2.0), Tangerine Peel (2.0), Ternate Pinellia (2.5), Amomum (2.0), Costusroot (2.0), Fresh Ginger (5.0)	Soup
	Liu-Jun-Zi Tang (六君子湯)[b]	Panax Ginseng (5.0), Atractylodes Rhizome (5.0), Indian Buead Tuckahoe (5.0), Ternate Pinellia (5.0), Honey-Fried Licorice Root (2.5), Tangerine Peel (2.5), Fresh Ginger (2.5), Common Jujube (2.5)	Pill
	Shen-Lin-Bai-Zhu San (蔘苓白朮散)[a]	White Hyacinth Bean (2.3), Panax Ginseng (3.0), Indian Buead Tuckahoe (3.0), Atractylodes Rhizome (3.0), Liquorice Root (3.0), Common Yan Rhizome (3.0), Lotus Seed (1.5), Balloonflower Root (1.5), Ma-Yuen Jobstears Seed (1.5), Amomum (1.5), Common Jujube (1.5)	Powder
	Bu-Zhong-Yi-Qi Tang (補中益氣湯)[b]	Astragalus Membranaceus (6.0), Panax Ginseng (4.0), Atractylodes Rhizome (2.0), Honey-Fried Licorice Root (4.0), Chinese Angelica (2.0), Tangerine Peel (2.0), Skunk Bugbane Rhizome (1.0), Chinese Thorawax Root (1.0), Fresh Ginger (3.0), Common Jujube (2.0)	Pill

[a]: Chiang et al. (2002).
[b]: Hsieh et al. (2013).

Appendix no 2: The average daily intake of Traditional Chinese Medicines prescription are according from many studies.

Prescription Effect	**Formula Name**	**Average Daily Intake (g/day)**
Blood	Ban-Long Wan(斑龍丸)[a]	
	Shu-Jing-Huo-Xue Tang(疏經活血湯)[b]	5.3[35] 4.4[36] 5.0[37]
	Zhigancao Tang(炙甘草湯)[b]	8.6[36] 3.65[38]
Blood/Painkiller	Tiaojing Wang(調經丸)[a]	
	Xuefu-Zhuyu Tang(血府逐瘀湯)[b]	4.8[36] 5.1[36] 4.5[38]
	Chuan-Xiong-Cha-Tiao San(川芎茶調散)[a]	5.1[35]
	Shang-Zhong-Xia-Tong-Yong-Tong-Feng Wan(上中下通用痛風丸)[a]	7.3[39]
Diaphoretic/Heat-cleaning	Huang-Lian-Jie-Du Tang(黃連解毒湯)[b]	
	Gan-Lu Yin (甘露飲)[b]	4.37[38]
	Xiao-Feng San(消風散)[b]	
	Hsiao-Chih Wan(消痣丸)[a]	
	Qingxin-Lianzi Tang(清心蓮子湯)[b]	
	Chai-Ge-Jie-Ji Tang(柴葛解肌湯)[b]	
	Gui-Zhi Tang(桂枝湯)[b]	
	Xiao-Qing-Long Tang(小青龍湯)[b]	4.03[40]
	Ge-Gen Tang(葛根湯)[b]	3.33[41] 3.66[40]
	Huo-Xiang-Zheng-Qi San(藿香正氣散)[b]	4.9[35] 3.32[41]
	Fangfeng-Tōng-Sheng San(防風通聖散)[b]	4.8[42]
	Ching-Fang-Pai-Tu Tang(荊防敗毒湯)[b]	
	Liu-Wei-Di-Huang Wan(六味地黃丸)[b]	5.3[36] 3.4[37] 6.44[45]
	Ba-Wei-Di-Huang Wan(八味地黃丸)[b]	
	Ji-Sheng-Shen-Qi Wan(濟生腎氣丸)[b]	4.8[36] 4.1[36] 5.3[37]
Kidney/Liver	Huan-Shao Dan(還少丹)[a]	
	Qi-Ju-Di-Huang Wan(杞菊地黃丸)[b]	3[43] 3.9[36] 4.78[38]
	Zhi-Bai-Di-Huang Wan(知柏地黃丸)[b]	7.8[37] 3.42[44] 4.27[38]
	Du-Huo-Ji-Sheng Tang(獨活寄生湯)[b]	5.6[35] 11.4[37]
Liver	Yang-Gan Wang(養肝丸)[a]	

	Long-Dan-Xie-Gan Tang(龍膽瀉肝湯)[b]	1.65[44]
Lung	Hua-Gai San(華蓋散)[b]	
	Er-Chen Tang(二陳湯)[b]	
	Ning-Sou Wang(寧嗽丸)[a]	
	Qing-Fei Tang(清肺湯)[b]	
	Zhi-Sou San(止嗽散)[b]	
	Xin-Yi-Qing-Fei Tang(辛夷清肺湯)[b]	3.11[41] 3.57[40]
	Ma-Xing-Gan-Shi-Tang(麻杏甘石湯)[b]	4.5[35] 2.1[36] 3.33[41]
Liver/Spleen	Si-Ni San(四逆散)[b]	5.2[42]
	Xiao-Yao San(逍遙散)[b]	
	Jia-Wei-Xiao-Yao San(加味逍遙散)[b]	2.4[43] 5.2[35] 4.1[37] 4.70[38]
Stomach/Spleen	Xiang-Sha-Liu-Jun-Zi Tang(香砂六君子湯)[b]	2.35[41] 2.71[40]
	Liu-Jun-Zi Tang(六君子湯)[b]	2.3[44]
	Shen-Lin-Bai-Zhu San(蔘苓白朮散)[a]	6.3[42]
	Bu-Zhong-Yi-Qi Tang(補中益氣湯)[b]	2.5[43] 3.5[40]

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