Original Article

Increased risks of chronic kidney disease associated with prescribed Chinese herbal products suspected to contain aristolochic acid

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SUMMARY:

Aim: Nephropathy associated with aristolochic acid (AA) has been documented by human and animal studies. Ancient Chinese herbology claimed to reduce toxicity in their mixtures. It was the objective of this study to determine the risk of chronic kidney disease (CKD) associated with AA-related Chinese herbal products (CHP) or mixtures of herbs in a national cohort.

Methods: A retrospective follow-up study was conducted, using a systematic random sample (200 000 people) in the National Health Insurance reimbursement database during 1997–2002. The incidence rates of CKD and end-stage renal disease (ESRD) were calculated for the whole sample and those that had used CHP suspected to contain AA. Cox regression models were constructed to control potential confounders, including age, sex, hypertension, diabetes mellitus, and use of non-steroidal anti-inflammatory drugs and acetaminophen.

Results: A total of 199 843 persons were included in the final analysis, 102 464 (51.3%) men and 97 379 (48.7%) women, with an average incidence rate of 1964/10⁶ person-years for CKD and 279/10⁶ person-years for ESRD. After controlling other risk factors, the hazard ratios for development of CKD seemed to increase for patients that had consumed more than 30 g Mu-Tong, and more than 60 g Fangchi.

Conclusion: Prescription of more than 30 g Mu-Tong or more than 60 g Fangchi CHP was associated with an increased risk of developing CKD. In addition to prohibiting the use of Guan-Mu-Tong and Guang-Fangchi, patients who have used these CHP should continue to be followed up.

KEY WORDS: aristolochic acid, Chinese herbal products, chronic kidney disease.

INTRODUCTION

The use of traditional and alternative medicines has been shown to be increasing during the last two decades.¹ However, the scientific evidence regarding the safety, efficacy and quality of such practices, as well as the regulatory controls being placed upon their usage, do not appear to run in

parallel with such popularity, as warned by the World Health Organization (WHO).² Chinese herbal products (CHP), which are synonymous with 'finished herbal product' or 'mixed herbal product' defined by the WHO,³ are currently one of the most common forms of Chinese medicine for people's use and are regularly reimbursed by the National Health Insurance (NHI) of Taiwan. People taking such herbs mixture and/or products seem to believe in the ancient herbology theory of Chinese medicine, in which different herbs are mixed together to counteract their toxicity and enhance efficacy.^{4–6} Thus, the traditional practice of pharmacovigilance² through passive reports from health-care workers and patients would be insufficient in the early detection of any adverse effects of Chinese medicine, and aristolochic acid (AA) nephropathy is a typical example.

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Aristolochic acid nephropathy (AAN) was first documented in young Belgian women who were taking one single Chinese herb, *Aristolochia fangchi*,^{7,8} which later proved nephrotoxic in clinical cases around the world, animal models, and by the detection of AA-DNA adducts in kidney and ureteral tissues of AAN patients.^{9–11} Although people in many countries, including China, Japan, Korea and Taiwan, have a long history of taking Chinese herbs, the first report of AAN was from physicians outside of these countries and led to a ban on the use of herbs containing AA.^{12,13}

Although medicines containing these herbs have been prohibited since 4 November 2003 in Taiwan,¹⁴ these herbs were once widely used and we suspected that AAN might play some role in the high incidence rate of end-stage renal disease (ESRD) in Taiwan.¹⁵ Although there are some case reports of nephropathy related to mixed Chinese herb usage,⁹ none have ever documented the association between incidence of chronic kidney disease (CKD) and taking prescribed CHP in a large cohort study. From a random sample of the NHI reimbursement database, we conducted this retrospective follow-up study to determine the risk of CKD from taking CHP prescribed by Chinese medicine doctors in Taiwan.

METHODS

Study population

In Taiwan, the NHI has been established since March 1995, covering over 96% of Taiwan residents.¹⁶ Standard mixtures of CHP have been included in the regular schedule of reimbursement. The National Health Research Institutes (NHRI) transformed the NHI reimbursement data to files for research,¹⁷ which provided detailed information about the usage of conventional drugs and CHP. The sample of this study was conducted through systematic random sampling of 200 000 people from the database of approximately more than 21 million people enrolled in the NHI. The data collection began in 1996, but it was more comprehensive after January 1997. The dataset of 200 000 people that we had access to included all the transactions of health-care services for each patient, such as diagnosis (coded by International Classification of Diseases, ICD-9), prescription drugs and doses (both conventional medicines and CHP), special treatment (including dialysis), and dates of such orders. We also obtained the registry files for patients with ESRD to verify the diagnosis of ESRD.

Follow-up time and new patients with ESRD or CKD and comorbidity

We defined the diagnosis of CKD as ICD-9 codes 585, 586, 588.8 and 588.9, which were either chronic renal insufficiency or failure. In general, such diagnoses are serious warnings to every patient and only made under support of clinical data consistent with the definition of CKD stages 3–5 of the Kidney Disease Outcomes Quality Initiative (K-DOQI).¹⁸ All 200 000 people sampled were followed from 1 January 1997 to 31 December 2002 to determine if any of them developed CKD or ESRD. Patients with CKD or ESRD at the first month of follow up were excluded because they were considered as prevalent cases. Moreover, the first day of CKD or ESRD for each patient had to be after 1 August 1997 to allow for 7 months of induction time for different risk factors. The patients with diabetes or hypertension were also ascertained

with a diagnosis number in ICD-9 before the first appearance of CKD or ESRD diagnosis.

Exposure assessment for conventional and traditional Chinese medicines

The reimbursement database contained all the details of prescribed conventional medicines, which included acetaminophen and the commercial names of 46 kinds of non-steroidal anti-inflammatory drugs (NSAIDs) shown in the Appendix. As phenacetin has been totally banned by the Department of Health since 1986, it was not included. Doses of each drug were determined according to the numbers of pills prescribed before the diagnosis of CKD or ESRD appeared. Cumulative doses were also calculated before CKD or ESRD.

According to the standard prescription recommended by the Committee on Chinese Medicine and Pharmacy (CCMP) in Taiwan,¹⁹ the following Chinese herb products may contain AA: Ma-Dou-Ling (*Fructus aristolochiae*), Tian-Xian-Teng (*Caulis aristolochiae*), Xi-Xin (*Asarum heterotopoides*), Guan-Mu-Tong (*Aristolochia manshuriensis*), Guang-Fangchi (*A. fangchi*) and Qing-Mu-Xiang (*Radix aristolochiae*). However, Guan-Mu-Tong, Guang-Fangchi and Qing-Mu-Xiang were once substituted under the names of Mu-Tong (*Akebia* sp.), Fangchi (*Stephania* sp.) and Mu-Xiang (*Radix Aucklandiae*), respectively, in Taiwan before 2003 because of similarities of gross morphology and common practices.¹⁹ In addition, according to an investigation by the Bureau of Food and Drug Analysis in Taiwan and some studies, approximately 89.2–100 % of Fangchi preparations were substituted by Guang-Fangchi^{20–22} and 84% of Mu-Tong by Guan-Mu-Tong.²³ There was no definite information about how much of Mu-Xiang was substituted by Qing-Mu-Xiang in the prescribed Chinese medicines. The above six herbs had their own single products or were one component of some mixed CHP. Each pharmaceutical company has published and submitted the detailed composition for every product, which was readily retrieved from the website of the Committee on Chinese Medicine and Pharmacy of the Department of Health.¹⁹ With this information, the original amounts of herbs in grams could be determined for each mixture of CHP. Then, the cumulative dose for each herb prescribed to an individual person before CKD could be calculated.

Statistical analyses

The incidence rate was summarized as the number of new CKD or ESRD patients/10⁶ person-years at risk. Potential risk factors, including age, sex, hypertension, diabetes mellitus, and prescriptions of NSAIDs, acetaminophen or any of the aforementioned Chinese herbs containing AA, were assessed for independent association with new occurrences of CKD or ESRD. The dose–response association between cumulative dose of Chinese herb and occurrence of CKD was tested by Mantel–Haenszel extension for the trend. For each potential risk factor, multivariate Cox proportional hazards models were constructed to estimate the relative risk and its 95% confidence interval (CI) for CKD or ESRD incidence and with stratification for age and sex. An estimate with the 95% CI that did not contain the number 1 was considered statistically significant. All the above analyses were conducted using the SAS ver. 9.2 software package (SAS Institute, Cary, NC, USA).

RESULTS

After excluding the prevalent cases and people with incomplete data or aged over 100 years, there were 199 843 persons included in the final analysis, with 102 464 (51.3%) men and 97 379 (48.7%) women. There were 30 044

(15.0%) persons with hypertension and 17 479 (8.8%) persons with diabetes mellitus. During the years 1997–2002, there were 14 064 176 outpatient visits, in which 112 264 persons (56.2% of all sampled), 1411 965 of whom had been prescribed CHP. The prescribed median daily doses of CHP were 0.5 g for Tian-Xian-Teng, 0.6 g for Mu-Xiang, 1 g for Mu-Tong, 1.2 g for Fangchi, 2.5 g for Ma-Dou-Ling and 0.9 g for Xi-Xin.

There were 2343 new CKD patients during the period 1 August 1997 to 31 December 2002 in the database, with 1208 (51.6%) men and 1135 (48.4%) women and a mean age of 59.3 ± 17.0 years. The average incidence rate was 1964/10⁶ person-years. There were 334 new ESRD patients during the period 1 August 1997 to 31 December 2002 in the database. The average incidence rate was 279/10⁶ person-years, with 183 (54.8%) women and 151 (45.2%) men and a mean age of 57.4 ± 14.8 years.

A crude analysis of observed numbers of newly diagnosed cases of CKD divided by numbers of population-at-risk for people taking different cumulative doses of analgesics or CHP suspected to contain AA is summarized in Table 1. It shows a dose–response association between taking Fangchi, NSAIDs or acetaminophen, and occurrence of CKD (Mantel–Haenszel extension test for trend, $P < 0.0001$) and provided us information to select a potential cumulative toxic dose for further stratified analysis, in which the cut-off points were chosen as follows: 30 g, 60 g, 100 g and 200 g for Mu-Xiang, Mu-Tong, Fangchi and Xi-Xin, respectively. There was no CKD case associated with more than 30 g Ma-Dou-Ling or Tian-Xian-Teng.

The numbers of new CKD cases, and hazard ratios (HR) calculated from Cox regression models for different risk factors (sex, age, diabetes, hypertension and cumulative doses for different drugs) fitted simultaneously are summarized in Table 2. The crude HR for development of CKD were significantly increased for patients of older age, with hypertension and diabetes, and consuming large doses of NSAIDs, acetaminophen, Mu-Tong and Fangchi with dose–response associations. There was multi-collinearity among hypertension, prescriptions of NSAIDs and acetaminophen and the correlation coefficients were generally in the range of 0.41–0.52, including that between age and hypertension (correlation coefficient, 0.52). We have constructed four Cox regression models to determine the associations. Table 2 shows that, except for the cells with small numbers, the adjusted HR for development of CKD were increased for patients prescribed more than 30 g Mu-Tong, or more than 60 g Fangchi for all four models, in which the estimates of regression coefficients were relatively stable for these two herbs. There were also increased adjusted HR with prescribing NSAIDs or acetaminophen in models 2 and 3, however, the multi-collinearity made the estimates of regression coefficients change a lot when hypertension was not included in the model. Because of a high correlation with age, there seems a lack of dose–response association between NSAIDs or acetaminophen and CKD in models 2 and 3. After stratification for age and sex, the HR obtained from Cox proportional hazards regression models indicated that young women seemed more likely to develop nephropathy, as in Table 3,

Table 1 Observed numbers (n) of newly developed cases of chronic kidney disease divided by numbers (N) of population-at-risk for people taking different cumulative doses of drugs in a total of 199 843 persons during 1997–2002

Cumulative dose (g) (pills for NSAIDs or acetaminophen)													
0		1–30		31–60		61–100		101–200		>200			
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	
Tian-Xian-Teng	2341/199 752	(1.17)	2/76	(2.63)	0/3	(0)	0/8	(0)	0/2	(0)	0/2	(0)	
Mu-Xiang	1999/170 225	(1.17)	285/25 179	(1.13)	38/2596	(1.46)	15/973	(1.54)	6/614	(0.98)	0/256	(0)	
Mu-Tong	1979/169 372	(1.17)	248/22 500	(1.10)	63/4331	(1.45)	27/1842	(1.47)	22/1264	(1.74)	4/534	(0.75)	
Fangchi†	1875/168 511	(1.11)	389/28 234	(1.38)	42/1892	(2.22)	18/643	(2.80)	10/387	(2.58)	9/176	(5.11)	
Ma-Dou-Ling	2338/199 301	(1.17)	5/340	(1.47)	0/116	(0)	0/45	(0)	0/32	(0)	0/9	(0)	
Xi-Xin	1810/156 289	(1.16)	400/32 281	(1.24)	74/5800	(1.28)	32/2656	(1.20)	17/1897	(0.90)	10/920	(1.09)	
0		1–500		501–1000		>1000							
NSAIDs†	153/21 424	(0.71)	1685/163 878	(1.03)	287/8590	(3.34)	218/5951	(3.66)					
Acetaminophen†	127/40 545	(0.31)	2063/154 467	(1.34)	133/4297	(3.10)	20/534	(3.75)					

†Significant for Mantel–Haenszel extension test. NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Number of new cases (n), crude and adjusted hazards ratios (HR), and 95% confidence intervals (CI) estimated from multivariate Cox regression model for chronic kidney disease on a random sample of the National Health Insurance database followed from 1997–2002

Variables	Case (n)	Crude HR	Model 1		Model 2		Model 3		Model 4	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Sex										
Female	1135	1.0	1.0		1.0		1.0		1.0	
Male	1208	1.0	1.1	0.99–1.2	1.0	0.96–1.1	1.1	0.98–1.2	1.1	0.97–1.1
Age										
<50 years	671	1.0	1.0		1.0		1.0		1.0	
50 to 64 years	639	5.5	2.8	2.5–3.2	4.4	3.9–4.9	4.2	3.8–4.7	2.8	2.5–3.2
65 to 99 years	1033	10.9	4.2	3.7–4.7	7.8	6.9–8.6	7.5	6.8–8.4	4.0	3.5–4.5
Hypertension										
No	927	1.0	1.0						1.0	
Yes	1416	8.8	3.0	2.7–3.4					3.1	2.8–3.4
Diabetes										
No	1470	1.0	1.0		1.0		1.0		1.0	
Yes	873	6.3	2.0	1.8–2.2	2.6	2.3–2.8	2.4	2.2–2.7	2.0	1.8–2.2
NSAIDs										
0 pills	153	1.0	1.0		1.0					
1–500 pills	1685	1.4	0.7	0.6–0.8	1.4	1.1–1.6				
501–1000 pills	287	4.7	0.6	0.5–0.8	1.5	1.2–1.8				
>1000 pills	218	5.2	0.5	0.4–0.6	1.2	0.9–1.4				
Acetaminophen										
0 pills	127	1.0	1.0				1.0			
1–500 pills	2063	4.3	2.6	2.1–3.2			2.8	2.3–3.4		
501–1000 pills	133	10.0	1.7	1.3–2.3			2.0	1.5–2.5		
>1000 pills	20	12.1	1.8	1.1–3.0			2.0	1.2–3.2		
Mu-Xiang										
0 g	1999	1.0	1.0		1.0		1.0		1.0	
1–30 g	285	1.0	1.0	0.8–1.1	1.1	0.8–1.5	0.9	0.8–1.1	1.0	0.8–1.1
31–60 g	38	1.2	1.0	0.8–1.5	1.1	0.7–1.9	1.1	0.8–1.5	1.1	0.8–1.5
61–100 g	15	1.3	1.1	0.7–1.8	1.1	0.7–1.9	1.1	0.7–1.9	1.1	0.7–1.9
101–200 g	6	0.8	0.6	0.3–1.4	0.6	0.3–1.4	0.6	0.3–1.4	0.6	0.3–1.4
>200 g	0	–	–	–	–	–	–	–	–	–
Mu-Tong										
0 g	1979	1.0	1.0		1.0		1.0		1.0	
1–30 g	248	0.9	1.0	0.8–1.1	1.0	0.9–1.2	1.0	0.9–1.1	1.0	0.9–1.1
31–60 g	63	1.2	1.3	1.03–1.8	1.4	1.1–1.8	1.4	1.1–1.8	1.4	1.1–1.8
61–100 g	27	1.3	1.4	0.96–2.1	1.5	1.04–2.3	1.5	1.03–2.3	1.4	0.97–2.1
101–200 g	22	1.5	1.7	1.1–2.6	1.8	1.1–2.8	1.7	1.1–2.7	1.7	1.1–2.6
>200 g	4	0.6	0.7	0.3–1.9	0.7	0.3–2.0	0.7	0.3–2.0	0.7	0.3–1.9
Fangchi										
0 g	1875	1.0	1.0		1.0		1.0		1.0	
1–30 g	389	1.2	1.0	0.9–1.2	1.1	0.9–1.2	1.0	0.9–1.2	1.0	0.9–1.2
31–60 g	42	2.0	1.3	0.98–1.9	1.4	0.99–1.9	1.4	0.98–1.9	1.3	0.96–1.8
61–100 g	18	2.5	1.8	1.1–2.8	1.9	1.2–3.0	1.8	1.1–2.9	1.7	1.1–2.7
101–200 g	10	2.3	1.4	0.8–2.7	1.5	0.8–2.8	1.5	0.8–2.7	1.4	0.7–2.7
>200 g	9	4.7	2.2	1.1–4.2	2.2	1.2–4.4	2.3	1.2–4.4	2.1	1.1–4.1
Xi-Xin										
0 g	1810	1.0	1.0		1.0		1.0		1.0	
1–30 g	400	1.1	0.9	0.8–1.04	0.9	0.8–1.05	0.9	0.8–1.03	0.9	0.8–1.04
31–60 g	74	1.1	0.8	0.6–1.1	0.8	0.6–1.05	0.8	0.6–1.02	0.8	0.6–1.1
61–100 g	32	1.0	0.7	0.5–1.01	0.7	0.5–1.0	0.7	0.5–1.0	0.7	0.5–1.0
101–200 g	17	0.8	0.5	0.3–0.8	0.5	0.3–0.8	0.5	0.3–0.8	0.5	0.3–0.8
>200 g	10	0.9	0.5	0.3–1.02	0.5	0.3–1.0	0.5	0.3–1.0	0.5	0.3–1.03

Model 1, all above variables fitted simultaneously; model 2, model 1 excluding hypertension and acetaminophen; model 3, model 1 excluding hypertension and NSAIDs; model 4, model 1 excluding NSAIDs and acetaminophen. NSAIDs, non-steroidal anti-inflammatory drugs.

Table 3 Number of new female cases (n) of chronic kidney disease by multivariate Cox regression model

Variable	Age (years) <50 (n = 353)			50–64 (n = 312)			65–99 (n = 470)		
	Case (n)	HR	95% CI	Case (n)	HR	95% CI	Case (n)	HR	95% CI
Mu-Xiang									
0 g	283	1		250	1		401	1	
1–30 g	57	0.8	0.6–1.1	52	1.1	0.8–1.5	54	0.9	0.7–1.3
31–60 g	10	1.2	0.6–2.4	5	0.8	0.3–2.0	9	1.3	0.7–2.7
61–100 g	3	0.8	0.3–2.6	2	1.0	0.2–4.0	4	1.6	0.6–4.5
101–200 g	0	–	–	3	1.8	0.5–5.8	2	1.2	0.3–5.0
>200 g	0	–	–	0	–	–	0	–	–
Mu-Tong									
0 g	265	1		263	1		413	1	
1–30 g	57	1.3	0.9–1.8	26	0.6	0.4–0.9	42	0.9	0.6–1.2
31–60 g	15	1.8	1.1–3.2	14	1.6	0.9–2.9	9	1.0	0.5–2.0
61–100 g	8	2.3	1.1–4.9	7	2.1	0.9–4.7	1	0.3	0.05–2.5
101–200 g	7	3.1	1.3–7.1	2	1.2	0.3–5.0	3	1.6	0.5–5.2
>200 g	1	0.9	0.1–6.9	0	–	–	2	1.9	0.5–8.0
Fangchi									
0 g	274	1		235	1		362	1	
1–30 g	66	1.2	0.9–1.6	64	0.8	0.6–1.1	90	1.2	0.9–1.5
31–60 g	5	1.4	0.6–3.4	7	1.1	0.5–2.5	13	1.8	1.03–3.3
61–100 g	3	2.1	0.7–6.8	3	1.7	0.5–5.3	4	1.8	0.6–5.0
101–200 g	2	2.4	0.6–9.8	1	0.9	0.1–6.3	1	0.5	0.1–3.9
>200 g	3	12.0	3.8–38.2	2	2.0	0.5–8.6	0	–	–

Hazards ratios (HR) and 95% confidence intervals (CI) obtained from Cox proportional hazards regression models with all variables (hypertension, diabetes and cumulative dosage of non-steroidal anti-inflammatory drugs and studied Chinese herbs) fitted simultaneously.

and a cumulative prescribed dose of more than 30–60 g Mu-Tong or over 60 g Fangchi seemed to associate with higher HR, although the numbers observed in different strata were not always big enough to show a statistical significance. There was a similar trend for the development of new ESRD cases in young women taking over 100 g Mu-Tong except that the numbers were smaller. There was no such finding for Fangchi presumably because of the small numbers after multiple stratifications.

Frequency distributions for different organ-system diseases during the pre-CKD period are summarized for CKD patients and reference subjects in Table 4. Musculoskeletal disorders, urinary disorders, gastrointestinal diseases, and neurological and mental disorders were more common in CKD patients, compared with those of non-CKD referents.

DISCUSSION

Taiwan has had remarkably high incidence and prevalence of CKD or ESRD since 2000, compared with other countries.^{24,25} Two previous studies revealed a close association between herbs and ESRD,^{26,27} and AAN was suspected to be a major risk factor for developing ESRD. Unlike Chinese herbs in some reports of AA-related nephropathy or Chinese herb nephropathy,^{7,9,26–29} CHP in Taiwan were produced by qualified pharmaceutical companies and were prescribed by formally trained doctors who received education of traditional Chinese medicine. To our limited knowledge, this is the first study of the general population showing

increased risks of CKD by regularly-prescribed CHP after control of potential confounding by other risk factors through multivariate modelling.

Because the data of this study were a systematic random sampling of approximately 200 000 subjects from the general population of Taiwan, the sampled persons were probably representative. To validate this assertion, we compared the occurrence rates of this database with previous large cohort studies in Taiwan. The incidence rate of ESRD in the database was 279/10⁶ person-years, which was similar to that of data provided by the Taiwan Society of Nephrology (227/10⁶ person-years in 1999)³⁰ and the Taiwan part of the international comparisons in the US Renal Data System (USRD) (288–365/10⁶ person-years from 1998–2002).¹⁵ The prevalence rates of hypertension and diabetes in the database seem also similar to those in the study from the Bureau of Health Promotion of Department of Health in Taiwan (15.1% vs 18.9% for hypertension; 8.9% vs 6.6% for diabetes).³¹ Table 2 shows that age, hypertension and diabetes are associated with increased incidence rates of CKD, which corroborates with previous studies from the USA and Taiwan,^{25,30,32,33} and excludes the potential confounding by these factors.

The crude analysis in Table 1 and crude HR in Table 2 appeared to have increased risks of CKD for NSAIDs and acetaminophen with dose-response associations, compatible with previous reports indicating the potential nephrotoxic effects of NSAIDs and acetaminophen.^{34,35} However, there was multi-collinearity among hypertension, age, prescriptions of NSAIDs and acetaminophen. Namely, people of old age or hypertensive were likely prescribed

Table 4 Prevalence of other diseases in patients with chronic kidney disease (CKD) before development of CKD compared with those of subjects without CKD

System diseases	CKD, n = 2343	(%)	Non-CKD, n = 197 500	(%)
Musculoskeletal disorders	1745	(74.5)	87 757	(44.4)
Upper respiratory diseases	1422	(60.7)	136 871	(69.3)
Gastrointestinal disorders	1262	(53.9)	102 557	(51.9)
Eye disorders	1233	(52.6)	88 805	(45.0)
Oral or teeth disorders	1222	(52.2)	128 277	(65.0)
Nervous disorders (excluding cerebrovascular accident)	914	(39.0)	30 526	(15.5)
Urinary disorders (excluding kidney diseases)	896	(38.2)	33 143	(16.8)
Mental disorders	721	(30.8)	27 534	(13.9)
Chronic obstructive pulmonary diseases	685	(29.2)	36 243	(18.4)
Chronic hepatitis or liver cirrhosis	563	(24.0)	19 080	(9.7)
Ear disorders	519	(22.2)	34 779	(17.6)
Diseases of female genital organs (including breast)	488	(20.8)	47 150	(23.9)
Cerebrovascular accident	387	(16.5)	8 358	(4.2)
Diseases of male genital organs	317	(13.5)	8 570	(4.3)
Blood disorders	253	(10.8)	6 503	(3.3)
Congestive heart failure	245	(10.5)	3 895	(2.0)

Non-CKD, persons without CKD.

NSAIDs or acetaminophen possibly because of headache and/or pain related to musculoskeletal disorders, as was demonstrated by the high correlation between prescriptions of NSAIDs and acetaminophen (correlation coefficient, 0.52). Fortunately, such a collinearity did not appear to influence the estimates of adjusted HR of CHP under study in all the alternative models (models 2–4 in Table 2) or confound the associations.

In this study, we found a significant dose–response trend between the amount of prescribed Fangchi and developing CKD, beginning at a cumulative dose of more than 30 gm (Table 1). Table 2 shows that the association persisted after controlling other risk factors for dosage of more than 60 g Fangchi, though this is not always evident in every stratified cell of Table 3. In Belgium, a cumulative dose of more than 100 g Guang-Fangchi was associated with an increased risk of ESRD.^{7,36} Because most AA nephropathy presents as rapidly progressive renal failure with regular continuous exposure of herbs containing AA, we think that AA-related CKD can mostly be induced by such a dosage (>60 g Fangchi) during 3 months to 3 years.

Similarly, taking a cumulative dose of more than 30 g Mu-Tong appeared associated with increased risk of CKD in Table 1; the trend seemed more evident among young women after controlling other potential confounders in Tables 2 and 3. The same association also showed up for ESRD, when the cumulative dose increased up to more than 100 g Mu-Tong. Guan-Mu-Tong was once found to be the major herb used in Chinese herbal mixtures associated with AAN in China, Japan and the UK.^{28,29,37,38} As 84% of Mu-Tong preparations were reported to be substituted by Guan-Mu-Tong during the study period,²³ we suspected that the nephrotoxicity resulted from AA-associated herbs and the manufacturing process of CHP did not seem to reduce

their nephrotoxicity. With over 22 million people insured during 1997–2002, it was estimated that 1500 new cases of CKD/year in Taiwan resulted from Chinese herbs.

It deserves our attention that young women, especially those less than 50 years old, were more likely to develop CKD if taking more than the threshold cumulative dose of Mu-Tong and Fangchi in our study. While CHP were popularly used among people in Taiwan, young woman were prescribed more often, as corroborated in another study based on the data of 2004³⁹ and in the outbreak of AAN in Belgium.^{7,8} Women also seemed predominant (66–98%) in AAN cases in Taiwan and China.^{26–29} We have no further conjectures for the phenomena, but recommend future studies to clarify them.

Mu-Xiang was suspected to be substituted by Qing-Mu-Xiang, which contains AA, but without any report to prove it. In our study, Mu-Xiang was not associated with developing CKD, indicating that Mu-Xiang might be less substituted by Qing-Mu-Xiang in CHP of Taiwan. Ma-Dou-Ling and Tian-Xian-Teng are herbs of the genus *Aristolochiae* and are expected to contain a similar concentration of AA to Guang-Fangchi given the same weight of crude drug.⁴⁰ Table 1 shows that no new CKD case was found for a cumulative dose of more than 30 g Ma-Dou-Ling or Tian-Xian-Teng, probably because of small numbers. In this study, there were 920 people who were prescribed with more than 200 g Xi-Xin cumulatively, but they did not show an increased risk of CKD (Table 1), which corroborated with the report that Xi-Xin (*Asarum*) used in CHP of Taiwan is mostly *A. heterotopoides* that contains a minute amount of AA with approximately 1/40 to 1/100 of that in *A. fangchi*.^{41,42}

Because Table 4 shows that people with CKD had higher proportions of pre-existing musculoskeletal and/or nervous

disorders, we propose that subjects with these disorders and prescribed NSAIDs or pain-relieving Chinese medicines should be closely monitored for their renal function.

There are some limitations to this study. First, because the reimbursement data file did not include detailed results from laboratory tests, we were unable to provide measurements of renal function for validation of CKD. However, because the diagnosis of ICD-9 codes 585, 586, 588.8 and 588.9 are a serious message to all patients, physicians generally avoid making such an announcement unless there are compatible laboratory reports of elevated serum creatinine. If we applied a more restrictive definition of CKD, or diagnoses made at least twice, we found that 2122 (90.6%) of the patients met the criteria, and the trend of AAN persisted, because a national representative survey showed that the prevalence of CKD stages 3–5 in people aged over 20 years in Taiwan was approximately 6.9%,⁴³ which amounts to 10 411 expected cases for our sample. We have identified, on average, 426 new cases/year. Assuming the average duration for CKD is 10–20 years, the prevalent cases would be 4260–8520, which indicates a low detection of this important disease through the NHI reimbursement database, compatible with the patients' low awareness.⁴³ To minimize underestimation, our definition of diagnosis of CKD seems acceptable. Second, we were unable to contact the patients because of the transformed ID numbers in the database, and we could not rule out additional consumption of nephrotoxic herbs or agents that the subjects might have taken without a prescription. However, because our NHI system has a comprehensive coverage and the co-payment was universally \$NT50, which was approximately equal to \$US1.5 and generally less expensive than herbs or alternative medicines sold in the market of Taiwan, the likelihood of subjects purchasing other AA-containing herbs or nephrotoxic drugs was probably very low. Unlike a clinical trial, we were not sure whether the patients had taken the prescribed medications. However, a large cumulative dose indicates that the patients continued receiving the prescriptions, which usually implies a positive response to medications or that they actually took the prescribed drugs. Even if the patient might not take all the medications, the result would only underestimate the effect of AA-related CHP.

In conclusion, Chinese herbal medicines are very popular in Taiwan, with approximately 56% of residents covered by NHI taking Chinese herbal medicines during the 6 years of our study. From the reimbursement database during the period 1997–2002, we found that subjects prescribed more than 30 g Mu-Tong or more than 60 g Fangchi from CHP were associated with an increased risk of developing CKD. This study provides some evidence to falsify the herbology theory of traditional Chinese medicine, in which different herbs are mixed together to counteract their toxicity. Therefore, in addition to prohibiting the use of Guan-Mu-Tong and Guang-Fangchi, we should continue following up patients who have taken CHP containing Mu-Tong or Fangchi. Future studies on possible increased risk on urothelial cancer among AA-related CHP users are needed to corroborate the hypothesis.

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APPENDIX

The commercial names of 46 kinds of non-steroidal anti-inflammatory drugs in the reimbursement database: acemetacin; acetylsalicylate (aspirin); alclofenac; alminoprofen; apronalide; avapryazone; benzydamine; celecoxib; diclofenac; diflunisal; dipyrrone (sulpyrin); ephedryl isopropylantipyrine; ethenzamide; etodolac; etofenamate; fenbufen; fenoprofen; flufenamate; flurbiprofen; glafenine; hydroxybutyric acid β -p-phenetidine; ibuprofen; indomethacin; ketoprofen; ketorolac tromethamine; meclofenamate; mefenamic acid; meloxicam; mepirazole; nabumetone; naproxen; niflumic acid; nimesulide; pantopon; phenylbutazone; piroxicam; propyphenazone; proxazole citrate; pyrabital; salsalate; sulindac; tenoxicam; tiaprofenic acid; tiaramide; tolfenamic acid; tolmetin.