Risks of Kidney Failure Associated With Consumption of Herbal Products Containing Mu Tong or Fangchi: A Population-Based Case-Control Study

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Background: Taiwan has a remarkably high incidence of end-stage renal disease (ESRD). The objective of this study is to determine the association between prescribed herbal products containing aristolochic acid and ESRD.

Study Design: Population-based case-control study.

Setting & Participants: All new ESRD cases in Taiwan and a simple random sample (200,000 people) drawn from the national health insurance reimbursement database in 1997-2002.

Predictor: Age; sex; hypertension; diabetes; cumulative doses of nonsteroidal anti-inflammatory drugs, acetaminophen, and adulterated herbal supplements potentially containing aristolochic acid before the development of chronic kidney disease; and indications for prescribing such herbs, including chronic hepatitis, chronic urinary tract infection, chronic neuralgia, or chronic musculoskeletal diseases.

Outcomes & Measurements: Occurrence of ESRD through construction of multiple logistic regression models.

Results: There were 36,620 new ESRD cases from 1998 through 2002. After exclusion of cases with chronic kidney disease diagnosed before July 1, 1997, there were 25,843 new cases of ESRD and 184,851 controls in the final analysis. Women, older age, hypertension, and diabetes were significantly associated with increased risks of the development of ESRD. After adjustment for known risk factors, cumulative doses >60 g of Mu Tong (OR, 1.47 [95% CI, 1.01-2.14] for 61-100 g; OR, 5.82 [95% CI, 3.89-8.71] for >200 g) or Fangchi (OR, 1.60 [95% CI, 1.20-2.14] for 61-100 g; OR, 1.94 [95% CI, 1.29-2.92] for >200 g) were associated with increased risk of the development of ESRD with a dose-response relationship. This relationship persisted when analyses were limited to participants who consumed <500 pills of nonsteroidal anti-inflammatory drugs and those without diabetes.

Limitations: No measurement of renal function, no contact with patients, over-the-counter sales were not recorded, and potential underestimation of exposure dose for cases and ORs.

Conclusions: Consumption of >60 g of Mu Tong or Fangchi from herbal supplements was associated with an increased risk of developing kidney failure.

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INDEX WORDS: Aristolochic acid; Chinese herb nephropathy; end-stage renal disease; Mu Tong; Fangchi.

Compared with other countries,[1,2] Taiwan has a remarkably high incidence and prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD). Multiple causes have been reported, including an increasing proportion of aged patients,[3] increased incidence of diabetic nephropathy,[3] high prevalence but low awareness for CKD,[4] and the comprehensive coverage of Taiwanese national health insurance.[3] In addition, there have been case reports of renal failure caused by Chinese herbal products[5,6] or herbs contain-

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ing aristolochic acid.[7,8] One study reported that regular users of Chinese herbal medicines had a 20% increased risk of developing CKD.[9] Because the cost of Chinese herbal products has been regularly reimbursed by Taiwanese national health insurance[10] and herbal products containing significant aristolochic acid, including Guan Mu Tong and Guang Fangchi, were once widely prescribed before they were prohibited on November 4, 2003, in Taiwan,[11] we suspected that these products might be associated with the increased risks of ESRD. However, there has been no strong epidemiologic evidence of aristolochic acid involvement in the development of ESRD in Taiwan. Xi Xin (*Asarum*) is still widely prescribed for many diseases in Asia, including Japan, Korea, China, and Taiwan. Because it still contains some amount of aristolochic acid, we were concerned about the potential nephrotoxicity of its cumulative dosage.

In Taiwan, national health insurance was established in March 1995 and covers >96% of Taiwan residents.[12] Standard mixtures of Chinese herbal products and conventional medicines have been included in the schedule of reimbursement. Using the national health insurance database, we reported that aristolochic acid from herbal products could be associated with an increased risk of developing CKD in a 200,000-people study in Taiwan.[13] However, we could not determine the risk of herbal products containing aristolochic acid for ESRD development because of the limited number of ESRD cases. Therefore, we conducted a case-control study to determine the risk and potential dose-response relationship of ESRD associated with prescribed herbal products containing aristolochic acid in Taiwan.

METHODS

Study Population and Data Collection

This study was started after approval by the Review Committee of the Committee on Chinese Medicine and Pharmacy, Department of Health, Taiwan. It was designed as a population-based case-control study to investigate the risk for Chinese herbal products associated with the occurrence of ESRD in Taiwan. The database used in the study was from the reimbursement system of national health insurance in Taiwan, which was established in March 1995 and covers >96% of all Taiwan residents.[12] Data collection began in 1996, but it was more complete after January 1997. The National Health Research Institutes transformed national health insurance reimbursement data to files for research.[14] These files provided detailed information for health care services for each patient, including all payments for outpatient visits, hospitalizations, and prescriptions. For each outpatient visit or hospitalization, the data contained up to 3-5 diagnoses coded under the *International Classification of Diseases, Ninth Revision*, prescription drugs and doses (both conventional medicines and herbal products), special treatments (such as dialysis), and dates of such orders. Because the identification number of each insured person was transformed and encrypted, privacy was protected.

Definitions of Cases and Controls

The process of selection of cases and controls in this study is summarized as a flow chart and shown in Fig 1. In the beginning, we obtained registry files for all patients with catastrophic illnesses from 1997-2002 in Taiwan, including ESRD (patients required dialysis therapy or renal transplant). Qualification for ESRD registration required a diagnosis of CKD with an irreversible creatinine level >8 mg/dL or creatinine level >6 mg/dL with diabetes mellitus as a comorbid condition. Because every patient registered in the database of catastrophic illnesses is eligible to have any copayment for dialysis therapy waived, the registry is comprehensive with excellent validity. We also defined the

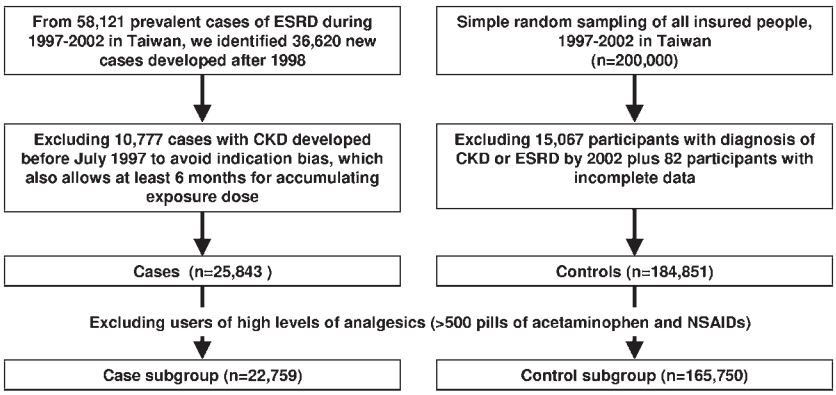

Figure 1. Flow chart illustrating the selection of cases and controls. Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

diagnosis of CKD as *International Classification of Diseases, Ninth Revision* codes 580-589, 250.4, 274.1, 403.01, and 404.02, which were consistent with the definition of CKD stages 1-5 according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI).[15]

There were 58,121 prevalent cases of ESRD in 1997-2002 in the database of the registry of catastrophic illnesses. We waited for 1 year to enroll patients with newly developed ESRD after January 1998, and 36,620 cases were collected. To prevent indication bias due to individuals taking herbs after the development of CKD, we deliberately excluded ESRD cases diagnosed as CKD before July 1, 1997, which allowed at least 6 months to accumulate the exposure dose. Thus, 25,843 new ESRD cases were included in the final analysis (Fig 1).

We then obtained data from 200,000 people selected through simple random sampling of all insured people (~21 million people) enrolled in the national health insurance in Taiwan.[14] The control population were followed up from January 1, 1997, to December 31, 2002. We excluded 15,067 participants with a diagnosis of CKD or ESRD plus 82 participants with incomplete data, which left 184,851 controls (Fig 1). Participants known to have diabetes mellitus or hypertension before being diagnosed with CKD also were identified in cases and controls.

Exposure Assessment

The reimbursement database contained all details for prescribed medicines, including both the generic and commercial names of conventional medicines and herbal products. To prevent confounding by indication of CKD, only medications (including herb products) prescribed before the diagnosis of CKD were considered as the exposure dose. Namely, cumulative doses of individual medications were summed from January 1997 to December 2002 for every control, whereas those for the case group were summed from January 1997 to the diagnosis of CKD. Phenacetin was banned by the Department of Health in 1986 and was not included. Users of high levels of analgesics were defined as individuals prescribed >500 pills in total of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) before the development of CKD.

According to the standard prescription recommended by the Committee on Chinese Medicine and Pharmacy in Taiwan,[16] herbal products produced before 2003 when new regulations were promulgated might include the following herbs containing aristolochic acid: Ma Dou Ling (*Fructus Aristolochiae*), Tian Xian Teng (*Caulis Aristolochiae*), Xi Xin (*Asarum heterotropoides*), Guan Mu Tong (*Aristolochia manshuriensis*), Guang Fangchi (*Aristolochia fangchi*), and Qing Mu Xiang (*Radix Aristolochiae*). Of these, Guan Mu Tong, Guang Fangchi, and Qing Mu Xiang were once sold under the names of Mu Tong (*Akebia* species), Fangchi (*Stephania* species), and Mu Xiang (*Radix Aucklandiae*), respectively. This was a frequent occurrence in Taiwan before 2003 because of similarities in gross morphologic characteristics and common practices.[16] It was shown that 89.2%-100% of Fangchi preparations were adulterated by Guang Fangchi,[17-19] and 84% of Mu Tong, by Guan Mu Tong.[20] There was no definite information about how much Qing Mu Xiang was substituted for Mu Xiang in prescribed Chinese medicines. These 6 herbs were taken as single products or were components of mixed herbal formulas recommended by ancient Chinese medicine books (eg, Mu Tong in the Long Dan Xie Gan mixture). Because prescription data from the national health insurance database could be linked directly to drug use by product number, we were able to identify all people who had used these herbal products. In addition, each pharmaceutical company has published and submitted the detailed composition of every product to the Committee on Chinese Medicine and Pharmacy for approval of registration. With this information, the original amounts of herbs in grams could be determined for each mixture of herbal products. The cumulative dose for each herb prescribed to an individual before the diagnosis of CKD then could be calculated.

Statistical Analyses

The incidence rate was summarized as the number of new patients with ESRD per 10^6 person-years at risk. The 2000 World Health Organization world standard population was used for calculation of the age-standardized incidence rate.[21] Potential risk factors, including age, sex, hypertension, diabetes mellitus, and cumulative doses of prescriptions of NSAIDs, acetaminophen, or any of the aforementioned herbs containing aristolochic acid before the development of CKD, were assessed for an independent association with new occurrences of ESRD through construction of univariate and multivariate logistic regression models. To control potential confounding by indications, we have included in the risk-estimate analysis diagnoses for which prescriptions of Mu Tong and Fangchi were recommended by the Committee on Chinese Medicine and Pharmacy[16]: namely, chronic hepatitis, chronic urinary tract infection, chronic neuralgia, or chronic musculoskeletal diseases. Because each prescription of herbal products provides 1-2 weeks of medication, we define patients with chronic hepatitis, chronic urinary tract infection, chronic neuralgia, or musculoskeletal diseases as having such a diagnosis if they received at least 12 prescriptions (ie, equivalent to 3-6 months) before the diagnosis of CKD. For each potential risk factor, the odds ratio (OR) and its 95% confidence interval for the occurrence of ESRD were estimated for logistic regression models after adjustment by other risk factors and propensity scores for prescribing Mu Tong, Fangchi, Mu Xiang, and Xixin.

Participants who ever used >500 pills of NSAIDs or acetaminophen were then excluded from both groups to form subgroups, and logistic regression models with propensity score adjustment were constructed again. An estimate with the 95% confidence interval that did not contain the number 1 was considered statistically significant. All these analyses were conducted using the SAS 9.2 edition software package (SAS Institute, www.sas.com).

RESULTS

In 1998-2002, crude and age-standardized incidence rates of ESRD were 329 and 323 events/10^6 person-years, respectively. The cumulative

Table 1. Frequency Distributions of Various Risk Factors for the Development of ESRD Stratified by Different Inclusion Criteria

Risk Factors	All Participants		Prescribed <500 Pills of Analgesics		Nondiabetic and Prescribed <500 Pills of Analgesics	
	Cases (n = 25,843)	Controls (n = 184,851)	Cases (n = 22, 759)	Controls (n = 165,750)	Cases (n = 11,063)	Controls (n = 158,487)
Sex						
Men	12,454	95,236	11,048	86,615	5,328	83,188
Women	13,389	89,615	11,711	79,135	5,735	75,299
Age (y)						
<30	782	82,189	765	80,431	674	79,731
30-49	6,178	63,285	5,871	58,299	3,839	55,644
50-69	12,217	27,528	10,626	20,159	3,951	17,335
70-99	6,666	11,849	5,497	6,861	2,599	5,777
Mean ± standard deviation	59.4 ± 14.5	34.7 ± 20.0	58.6 ± 14.7	32.3 ± 18.7	55.6 ± 16.7	31.4 ± 18.3
Hypertension						
No	7,018	161,921	6,711	152,948	5,069	148,530
Yes	18,825	22,930	16,048	12,802	5,994	9,957
Diabetes						
No	12,030	172,157	11,063	158,487		
Yes	13,813	12,694	11,696	7,263		
Chronic hepatitis						
No	25,260	181,856	22,277	164,059	10,892	157,213
Yes	583	2,995	482	1,691	171	1,274
Chronic urinary tract infection						
No	25,485	183,404	22,515	165,089	10,953	157,923
Yes	358	1,447	244	661	110	564
Chronic neuralgia						
No	24,169	180,038	21,726	164,064	10,760	157,059
Yes	1,674	4,813	1,033	1,686	303	1,428
Musculoskeletal disease						
No	20,884	158,503	19,668	152,278	9,662	146,730
Yes	4,959	26,348	3,091	13,472	1,401	11,757
NSAIDs (no. of pills)						
0-500	23,469	173,984	22,759	165,750	11,063	158,487
501-1,000	1,622	6,670	—	—	—	—
1,001-2,000	652	3,120	—	—	—	—
>2,000	100	1,077	—	—	—	—
Acetaminophen (no. of pills)						
0-500	25,566	181,541	22,759	165,750	11,063	158,487
501-1,000	196	2,996	—	—	—	—
1,001-2,000	70	307	—	—	—	—
>2,000	11	7	—	—	—	—

(Continued)

Table 1 (Cont'd). Frequency Distributions of Various Risk Factors for the Development of ESRD Stratified by Different Inclusion Criteria

Risk Factors	All Participants		Prescribed <500 Pills of Analgesics		Nondiabetic and Prescribed <500 Pills of Analgesics	
	Cases (n = 25,843)	Controls (n = 184,851)	Cases (n = 22, 759)	Controls (n = 165,750)	Cases (n = 11,063)	Controls (n = 158,487)
Mu Tong (g)						
0	22,188	157,939	19,542	142,636	9,385	136,596
1-30	2,542	20,122	2,227	17,404	1,097	16,518
31-60	492	3,729	432	3,157	227	2,960
61-100	226	1,569	201	1,318	116	1,250
101-200	209	1,054	182	883	120	829
>200	186	438	175	352	118	334
Fangchi (g)						
0	21,985	157,543	19,493	143,668	9,533	137,798
1-30	3,145	24,868	2,661	20,318	1,247	19,061
31- 60	362	1,528	305	1,119	142	1,035
61-100	169	492	142	361	59	335
101-200	116	295	99	202	45	187
>200 g	66	125	59	82	37	71
Xi Xin (g)						
0	20,853	146,239	18,438	133,205	8,849	127,726
1-30	3,799	28,895	3,274	24,510	1,612	23,159
31-60	571	5,043	501	4,162	290	3,941
61-100	284	2,279	242	1,863	124	1,771
101-200	202	1,623	183	1,373	109	1,295
201-500	106	652	94	537	62	504
501-1,000	19	96	19	80	12	74
>1,000	9	24	8	20	5	17
Mu Xiang (g)						
0	22,117	158,666	19,455	143,484	9,453	137,405
1-30	3,108	22,411	2,752	19,179	1,314	18,189
31-60	338	2,211	295	1,817	151	1,699
61-100	159	834	149	695	80	662
101-200	73	512	66	409	42	384
>200	48	217	42	166	23	148

Abbreviations: ESRD, end-stage renal disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

incidence rate from age 0-89 years was 0.056. Table 1 lists frequency distributions of various risk factors for the development of ESRD stratified by different inclusion criteria. After excluding participants ever prescribed >500 pills of acetaminophen and NSAIDs, 22,759 cases and 165,750 controls remained. To avoid potential confounding by diabetic nephropathy, we further restricted the analysis to participants without diabetes, including 11,063 cases and 158,487 controls. Table 2 lists results of univariate and multivariable logistic regression models indicating that women, older age, hypertension, and diabetes were significantly associated with increased risks of the development of ESRD in all participants. After adjustment for other major risk factors, there was a decreased risk for NSAIDs and increased risk for >2,000 pills of acetaminophen. However, >60 g of Mu Tong or Fangchi was consistently associated with increased risks of development of ESRD after adjustment for identified risk factors, and there seemed to be a dose-response relationship (Fig 2). After excluding participants who were ever prescribed >500 pills of acetaminophen and NSAIDs, women, older age, hypertension, and diabetes still showed significant associations with increased risks of

Table 2. Univariate and Multivariable Adjusted ORs for the Development of ESRD

Risk Factors	All Participants		Multivariable Adjusted OR (95% CI)	
	Univariate OR (95% CI)	Multivariable Adjusted OR (95% CI)	Prescribed <500 Pills of Analgesics	Nondiabetic and Prescribed <500 Pills of Analgesics
Sex				
Men	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Women	1.14[a] (1.11-1.17)	1.12[a] (1.07-1.17)	1.16[a] (1.11-1.21)	1.24[a] (1.18-1.31)
Age (y)				
<30	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
30-49	10.26[a] (9.52-11.06)	6.79[a] (6.25-7.38)	6.46[a] (5.92-7.04)	6.70[a] (6.10-7.35)
50-69	46.63[a] (43.32-50.19)	14.28[a] (13.10-15.58)	13.65[a] (12.47-14.95)	14.10[a] (12.77-15.57)
70-99	59.11[a] (54.75-63.81)	16.17[a] (14.79-17.67)	17.61[a] (16.03-19.34)	20.54[a] (18.55-22.75)
Hypertension				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	18.94[a] (18.37-19.53)	6.95[a] (6.68-7.22)	7.70[a] (7.39-8.03)	7.60[a] (7.23-7.99)
Diabetes				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	—
Yes	15.57[a] (15.11-16.05)	4.90[a] (4.72-5.10)	5.58[a] (5.34-5.83)	—
Chronic hepatitis				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	1.40[a] (1.28-1.53)	0.42[a] (0.38-0.48)	0.53[a] (0.46-0.61)	0.76[a] (0.62-0.92)
Chronic urinary tract infection				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	1.78[a] (1.59-2.00)	0.86 (0.74-1.01)	1.07 (0.87-1.31)	1.26 (0.98-1.62)
Chronic neuralgia				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	2.59[a] (2.45-2.74)	1.16[a] (1.07-1.25)	1.34[a] (1.20-1.50)	1.14 (0.98-1.33)
Musculoskeletal disease				
No	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Yes	1.43[a] (1.38-1.48)	0.41[a] (0.39-0.43)	0.55[a] (0.48-0.63)	0.67[a] (0.57-0.80)
NSAIDs (no. of pills)				
0-500	1.0 (reference)	1.0 (reference)	—	—
501-1,000	1.80[a] (1.71-1.91)	0.51[a] (0.48-0.55)	—	—
1,001-2,000	1.55[a] (1.42-1.69)	0.34[a] (0.31-0.38)	—	—
>2,000	0.69[a] (0.56-0.85)	0.17[a] (0.13-0.21)	—	—
Acetaminophen (no. of pills)				
0-500	1.0 (reference)	1.0 (reference)	—	—
501-1,000	0.47[a] (0.40-0.54)	0.12[a] (0.10-0.14)	—	—
1,001-2,000	1.62[a] (1.25-2.10)	0.51[a] (0.38-0.69)	—	—
>2,000	11.14[a] (4.32-28.75)	4.06[a] (1.34-12.35)	—	—
Mu Tong (g)				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1-30	0.90[a] (0.86-94)	1.12 (0.86-1.47)	1.07 (0.79-1.47)	1.10 (0.75-1.62)
31-60	0.94 (0.85-1.03)	1.16 (0.83-1.62)	1.09 (0.74-1.60)	1.21 (0.76-1.94)
61-100	1.03 (0.89-1.18)	1.47[a] (1.01-2.14)	1.40 (0.91-2.16)	1.55 (0.92-2.60)

(Continued)

Table 2 (Cont'd). Univariate and Multivariable Adjusted ORs for the Development of ESRD

	All Participants		Multivariable Adjusted OR (95% CI)	
Risk Factors	Univariate OR (95% CI)	Multivariable Adjusted OR (95% CI)	Prescribed <500 Pills of Analgesics	Nondiabetic and Prescribed <500 Pills of Analgesics
Mu Tong (g) (Cont'd)				
101-200	1.41[a] (1.22-1.64)	2.14[a] (1.47-3.11)	2.09[a] (1.36-3.22)	2.42[a] (1.45-4.05)
>200	3.02[a] (2.55-3.59)	5.82[a] (3.89-8.71)	6.33[a] (4.02-9.98)	6.17[a] (3.62-10.53)
Fangchi (g)				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1-30	0.91[a] (0.87-0.94)	0.68[a] (0.58-0.78)	0.69[a] (0.59-0.81)	0.66[a] (0.54-0.80)
31-60	1.70[a] (1.51-1.91)	1.14 (0.91-1.44)	1.23 (0.95-1.58)	1.12 (0.83-1.52)
61-100	2.46[a] (2.07-2.93)	1.60[a] (1.20-2.14)	1.65[a] (1.19-2.28)	1.39 (0.95-2.05)
101-200	2.82[a] (2.27-3.50)	1.62[a] (1.17-2.23)	1.77[a] (1.23-2.57)	1.47 (0.95-2.27)
>200	3.78[a] (2.81-5.10)	1.94[a] (1.29-2.92)	2.28[a] (1.44-3.63)	2.40[a] (1.43-4.04)
Xi Xin (g)				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1-30	0.92[a] (0.89-0.96)	0.79[a] (0.67-0.93)	0.85 (0.70-1.03)	0.81 (0.64-1.02)
31-60	0.79[a] (0.73-0.87)	0.55[a] (0.41-0.74)	0.70[a] (0.50-0.98)	0.60[a] (0.40-0.90)
61-100	0.87[a] (0.77-0.99)	0.49[a] (0.35-0.69)	0.60[a] (0.41-0.90)	0.49[a] (0.30-0.79)
101-200	0.87 (0.75-1.01)	0.45[a] (0.31-0.66)	0.58[a] (0.38-0.90)	0.52[a] (0.31-0.88)
201-500	1.14 (0.93-1.40)	0.45[a] (0.29-0.69)	0.53[a] (0.33-0.85)	0.46[a] (0.26-0.82)
501-1,000	1.39 (0.85-2.27)	0.41[a] (0.20-0.84)	0.56 (0.25-1.22)	0.53 (0.22-1.31)
>1000 g	2.63 (1.22-5.66)	0.43 (0.16-1.13)	0.44 (0.15-1.30)	0.44 (0.12-1.60)
Mu Xiang (g)				
0	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
1-30	1.00 (0.96-1.04)	1.37[a] (1.18-1.59)	1.34[a] (1.13-1.59)	1.37[a] (1.12-1.68)
31-60	1.10 (0.98-1.23)	1.23 (0.98-1.54)	1.24 (0.96-1.59)	1.18 (0.88-1.58)
61-100	1.37[a] (1.15-1.62)	1.40[a] (1.05-1.85)	1.56[a] (1.15-2.13)	1.30 (0.91-1.85)
101-200	1.02 (0.80-1.31)	1.01 (0.71-1.43)	1.18 (0.80-1.74)	1.20 (0.77-1.87)
>200	1.59[a] (1.16-2.17)	1.33 (0.86-2.04)	1.40 (0.86-2.28)	1.48 (0.84-2.61)

Note: ORs adjusted for propensity scores of prescribing herbal supplements containing 4 different herbs. Multivariable-adjusted ORs were adjusted for other variables in this table.

Abbreviations: CI, confidence interval; ESRD, end-stage renal disease; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

[a]Statistically significant.

the development of ESRD. Adjusted ORs consistently showed significant increased risks for patients prescribed >100 g of Mu Tong or >60 g of Fangchi, and the dose-response relationships persisted. In the nondiabetic group, we still found a consistent association for patients consuming >100 g of Mu Tong or >200 g of Fangchi. Adjusted ORs were not significantly increased for patients with high cumulative doses of Mu Xiang, Xi Xin, Ma Dou Ling, or Tian Xian Teng.

Frequencies and indications for prescribed herbal products containing Mu Tong or Fangchi in patients with ESRD with cumulative doses >60 g of Mu Tong or Fangchi before CKD development are listed in Table 3. The most common herbal product containing Mu Tong was Long Dan Xie Gan mixture, which usually was used to treat hepatitis, urinary tract infection, vaginitis, and oral ulcer. The most common herbal product containing Fangchi was Shu Jing Huo Xue Tang, which usually was prescribed to treat arthralgia and neuralgia.

DISCUSSION

This population-based study is the first to document the dose-response association between Chinese herbal products and ESRD, showing the increased risks associated with use of >60 g of

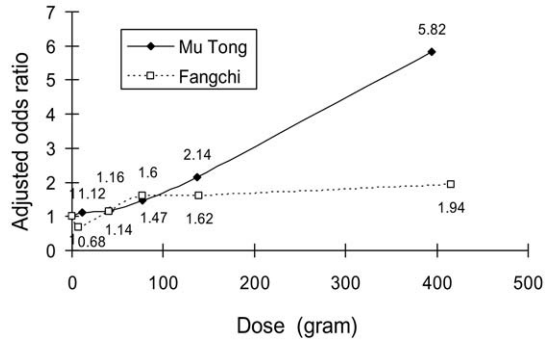

Figure 2. Dose-response relationships between adjusted odds ratios for the occurrence of end-stage renal disease and doses (in grams) of Mu Tong and Fangchi.

Mu Tong or Fangchi in 1997-2002. Because all new cases were included and controls in this study were selected from simple random sampling from all the population of Taiwan, there was no selection bias. Because all other major risk factors for ESRD, including age, sex, hypertension, and diabetes, and indications plus propensity scores for prescribing herbal products were controlled through multivariate modeling, they cannot explain this association (Table 2). Because there might be interaction and confounding by indication between herbal products and analgesics, we excluded the latter to reanalyze the data and showed that results were the same (Table 2). Further exclusion of participants with diabetes still showed a consistent result (Table 2). Finally, because the reimbursement database collects all prescription information prospectively, there is no recall bias for the intake doses of various herbal products. Thus, we tentatively concluded that a dose-response relationship for Chinese herbal products and ESRD exists, which implies that the manufacturing process of these herbal products did not get rid of the potential nephrotoxicity of aristolochic acid contained in herbs.

To validate the representativeness of this database, we compared occurrence rates of major diseases in this study with previous large cohort studies in Taiwan. Prevalence rates of hypertension and diabetes in controls were similar to those in a national survey conducted by the Bureau of Health Promotion of the Department of Health of Taiwan (12.4% vs 18.9% for hypertension; 6.9% vs 6.6% for diabetes).[22] The incidence rate and sex ratio of ESRD in the database

Table 3. Prescribed Herb Products Containing Mu Tong or Fangchi in ESRD Patients With Cumulative Dose >60 g of Mu Tong or Fangchi Before the Development of CKD

Product	No.	%	Indication
Prescriptions containing Mu Tong (n = 9,608)			
Long Dan Xie Gan	3,919	40.8	Hepatitis, UTI, vaginitis, oral ulcer
Shin Yi San	1,755	18.3	Rhinitis, URI
Ba Zheng San	763	7.9	UTI, vaginitis
Xiao Feng San	709	7.4	Allergy, eczema
Ba Wei Dai Xia Fang	543	5.7	UTI, vaginitis
Gan Lou Xiao Du Dan	573	6.0	Hepatitis, UTI
Dao Chi San	524	5.5	UTI, oral ulcer
Dang Gui Si Ni Tang	453	4.7	Headache, pain, dysmenorrhea
Mu Tong	296	3.1	Anti-inflammation, dysuria
Guo Qi Yin	36	0.4	Dysmenorrhea
Xiao Ji Yin Zi	34	0.4	UTI, urolithiasis
Ju He Wan	3	0.03	Hernia, scrotum swelling
Prescriptions containing Fangchi (n = 2,660)			
Shu Jing Huo Xue Tang	1,306	49.1	Arthralgia, neuralgia
Shang Zhong Xia Tong Yong Tong Feng	492	18.5	Arthralgia, neuralgia
Fang Ji Huang Qi Tang	409	15.4	Arthralgia, edema, dysmenorrhea
Fang Ji (Fangchi)	206	7.7	Arthralgia, edema
Xiao Xu Ming Tang	152	5.7	Hypertension, arthralgia, neuralgia, CVA
Jie Geng Tang	53	2.0	Bronchitis, pneumonia, cough
Mu Fang Ji Tang	42	1.6	Bronchitis, heart failure, edema

Abbreviations: CKD, chronic kidney disease; CVA, cerebrovascular accident; ESRD, end-stage renal disease; UTI, urinary tract infection; URI, upper respiratory tract infection.

were 323 events/10^6 person-years and 0.93, respectively. These were similar to data provided by the Taiwan Society of Nephrology (292-331 events/10^6 person-years from 1998-2001 and 0.91)[3] and the Taiwan section of international comparisons in the US Renal Data System (288-365 events/10^6 person-years from 1998-2002).[1] As listed in Tables 1 and 2, age, hypertension, and diabetes are associated with increased ORs for ESRD, which corroborates with previous studies from the United States and Taiwan.[3,23,24]

In this study, there was reduced risk for NSAIDs and an increased risk for >2,000 pills of acetaminophen associated with the occurrence of ESRD, although crude analysis showed increased risks of ESRD for NSAIDs (500-2,000 pills) and acetaminophen (>1,000 pills; Table 2). The association between analgesic consumption and increased risk of kidney disease is somewhat controversial, except in the case of phenacetin,[25-27] as indicated in the consensus report of the Ad Hoc Committee of the International Study Group on Analgesics and Nephropathy.[28] A possible explanation is the multicolinearity among age, hypertension, diabetes, and prescriptions of NSAIDs and acetaminophen; that is, people with old age, hypertension, or diabetes were likely to be prescribed NSAIDs or acetaminophen, possibly because of headache and/or pain related to musculoskeletal disorders (suggested by the high correlation between prescriptions of NSAIDs and acetaminophen [correlation coefficient, 0.47] and between prescriptions of NSAIDs and musculoskeletal diseases [correlation coefficient, 0.47] in this study). Analgesic nephropathy has been associated with cumulative doses of >5,000 pills' ingestion during a period >5 years.[26,27] In this study, almost all participants consumed <2,000 pills of analgesics before ESRD during the study period of <6 years or the window period of 1997-2002. Therefore, to avoid misinterpretation for these potential interactions, we deliberately excluded participants prescribed high doses of analgesics. The resulting data still showed an increased risk of ESRD associated with cumulative doses >60 g of Mu Tong or Fangchi (Table 2).

To explore the potential mechanism of nephrotoxicity associated with herbal products in this study, we tried to exclude participants with diabetes, in whom the mechanism of disease is glomerular vascular sclerosis. Because aristolochic acid causes interstitial nephritis,[8] we predicted that the ESRD cases that resulted from aristolochic acid should persist after excluding diabetic patients, which was corroborated in Table 2.

In Taiwan, 1 g of Guan Mu Tong and of Guang Fangchi were estimated to contain 2.59 and 2.04 mg of aristolochic acid, respectively.[17,19] This appeared slightly higher than the Dutch and Belgian reports (2.1 and 1.56 mg of aristolochic acid per 1 g of Mu Tong and Fangchi).[29,30] Thus, a cumulative dose of 60 g of Mu Tong and Fangchi in Taiwanese herbal products would supply 155 and 122 mg of aristolochic acid, respectively. This is similar to the dose of 100 g of Fangchi (Guang Fangchi) associated with ESRD in the Belgian cluster of Chinese herb nephropathy.[31] With prescribed median daily doses of 1 g for Mu Tong and 1.2 g for Fangchi in herbal products,[13] exposure to >155 mg of aristolochic acid could be achieved in ~2 months and could be expected to result in rapidly progressive renal failure similar to that of patients in the Belgian cluster of herb nephropathy.[8,31] Thus, allowing an induction period of 1-6 years in this study would detect most participants with ESRD caused by aristolochic acid if these 2 herbs were continually prescribed.

Although both Mu Xiang and Xi Xin have been very popularly used in Chinese herbal medicine, neither was associated with the development of ESRD, which was consistent with our previous cohort study of the occurrence of CKD.[13] It indicates that Mu Xiang in herbal products of Taiwan might not be substituted by Qing Mu Xiang.[29,32] Xi Xin (*Asarum*) used in herbal products in Taiwan has been mostly *Asarum heterotropoides*, which contains minute amounts of aristolochic acid (~0.009-0.042 mg of aristolochic acid per 1 g of Xi Xin; ~1/50-1/200 of that in *Aristolochia fangchi*).[29,33,34] Moreover, Xi Xin usually is prescribed in small dosages to avoid causing arrhythmia or heart disease.[35] With the prescribed median daily dose of 0.9 g for Xi Xin in our study,[13] exposure to >155 mg of aristolochic acid would take >10 years. Therefore, we were unable to detect an association between consumption of herbal products containing Xi Xin (*Asarum heterotropoides*) and ESRD, but we must still give careful atten-

tion to its use and provide long-term follow-up for participants regularly consuming it.

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 and ESRD. However, because approval for a registered catastrophic illness is followed by a full waiver of copayment, the diagnosis of ESRD is considered very serious and accurate. The definition of CKD is applied only for excluding control participants and calculating the cumulative doses of medications for cases, which would prevent overestimation of the exposure. Second, we were unable to contact patients because of the transformed identification numbers in the database, and we could not rule out additional consumption of nephrotoxic herbs or agents that participants might have used without a prescription. However, because the Taiwanese national health insurance system has comprehensive coverage and the copayment was universally 50 NT (new Taiwan) dollars (equal to ~$1.5 US) and generally less expensive than herbs sold over the counter in Taiwan, the likelihood of participants continually spending lots of money to purchase other aristolochic acid–containing herbs or nephrotoxic drugs or alternative medicines might be low. Unlike a clinical trial, we were not sure whether patients had used the prescribed medications. However, a large cumulative dose indicates that the patients continued receiving the prescriptions, which usually implies consumption of prescribed medication with a positive response. If the patient did not use all prescribed medications, the result would only underestimate the effect of aristolochic acid–related Chinese herbal products. Finally, we have taken a conservative stand to estimate the cumulative exposure doses for cases only up to the development of CKD, whereas those for controls were accumulated for the entire study period, or 1998-2002. Thus, the prevalence rate of prescribed herbal products and possibly the calculated OR most likely underestimate the real condition.

In conclusion, herbal products containing significant amounts of aristolochic acid, including Mu Tong and Fangchi, contributed to the high incidence and prevalence of CKD or ESRD in Taiwan from 1997-2002. Using >60 g of Mu Tong or Fangchi from herbal products was associated with an increased risk of developing ESRD. In 1998-2002, there were 949 new cases of ESRD in Taiwan in which the patient ever consumed Fangchi or Mu Tong before the diagnosis of CKD, representing 3.7% of all new patients with ESRD. If we applied calculation of the attributable fraction stratified by different prevalence rates and adjusted risk ratios for exposure doses among cases, namely, 61-100, 101-200, and >200 g for Mu Tong and Fangchi, the population-attributable risks for ESRD caused by Mu Tong and Fangchi were 1.3% and 0.54%, respectively, although this might be an underestimation. People with preexisting musculoskeletal disorders, urinary disorders, female genital disorders, oral disorders, or chronic hepatitis had a higher likelihood of receiving a prescription for Mu Tong or Fangchi when they asked for Chinese medicines (Table 3). The study thus provides the critical dosages of herbs containing aristolochic acid associated with an elevated risk of developing ESRD, which might be useful for establishing the limits of consumption for herbs or food containing a low aristolochic acid amount.[36] In addition to the ban, we also recommend universal surveillance of herbs or Chinese herbal products containing aristolochic acid to prevent ESRD.

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