


RESEARCH ARTICLE

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# The utilization of traditional Chinese medicine in patients with dysfunctional uterine bleeding in Taiwan: a nationwide population-based study

Yi-Rong Lin<sup>1</sup>, Mei-Yao Wu<sup>2</sup>, Jen-Huai Chiang<sup>3,4</sup>, Hung-Rong Yen<sup>1,2,5,6,7\*</sup>  and Su-Tso Yang<sup>1,8\*</sup>

## Abstract

**Background:** Many patients with gynecological disorders seek traditional medicine consultations in Asian countries. This study intended to investigate the utilization of traditional Chinese medicine (TCM) in patients with dysfunctional uterine bleeding (DUB) in Taiwan.

**Methods:** We analyzed a cohort of one million individuals randomly selected from the National Health Insurance Research Database in Taiwan. We included 46,337 subjects with newly diagnosed DUB (ICD-9-CM codes 626.8) from January 1, 1997 to December 31, 2010. The patients were categorized into TCM seekers and non-TCM seekers according to their use of TCM.

**Results:** Among the subjects, 41,558 (89.69%) were TCM seekers and 4,779 (10.31%) were non-TCM seekers. Patients who were younger tended to be TCM seekers. Most of the patients had also taken Western medicine, especially tranexamic acid and non-steroidal anti-inflammatory drugs (NSAIDs). More than half of TCM seekers (55.41%) received combined treatment with both Chinese herbal remedies and acupuncture. The most commonly used TCM formula and single herb were Jia-Wei-Xiao-Yao-San (Bupleurum and Peony Formula) and Yi-Mu-Cao (Herba Leonuri), respectively. The core pattern of Chinese herbal medicine for DUB patients consisted of Jia-Wei-Xiao-Yao-San, Xiang-Fu (Rhizoma Cyperi), and Yi-Mu-Cao (Herba Leonuri).

**Conclusions:** TCM use is popular among patients with DUB in Taiwan. Further pharmacological investigations and clinical trials are required to validate the efficacy and safety of these items.

**Keywords:** Complementary and alternative medicine, Chinese herbal medicine, Dysfunctional uterine bleeding, National Health Insurance Research Database, Traditional Chinese medicine

## Background

Dysfunctional uterine bleeding (DUB) is defined as excessive, prolonged, frequent, and unpattern bleeding from the uterine in the absence of any structural etiology [1]. In order to standardize the terminology, diagnosis and investigations of abnormal uterine bleeding, the FIGO classification system (PALM-COEIN) was published in 2011 [2].

DUB is considered as non-structural abnormal uterine bleeding.

DUB significantly and negatively impacts the patient's physical and social quality of life. It may put patients at risk for developing anemia, fatigue, and depression. Patients with heavy menstrual bleeding had higher hospitalization rates, emergency room visits, and outpatient visits [3]. Otherwise, heavy bleeding had significant economic implications for women because it was associated with work loss [4].

Current treatments for DUB include combined oral contraceptives, progestogens, non-steroidal anti-inflammatory drugs (NSAIDs), tranexamic acid, gonadotropin-releasing hormone analogues, danazol, and levonorgestrel-releasing

\* Correspondence: hungrongyen@gmail.com; yangst@mail.cmu.edu.tw  
<sup>1</sup>Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of Chinese Medicine, China Medical University, 91 Hsueh-Shih Rd. North District, Taichung 404, Taiwan  
Full list of author information is available at the end of the article

intra-uterine system (LNG IUS) [5]. Endometrial ablation and hysterectomy are the surgical options for DUB. Surgical treatments are recommended in the presence of medical therapy failure, severe anemia, or other concomitant uterine pathology [6]. However, tranexamic acid not only increases the risk of thrombosis but also has side effects such as headache, anemia, and fatigue [7]. In addition to the risks of blood loss and ureteric injury, hysterectomy is not suitable for the women with fertility plan. Current conventional treatments do not fit the need of all DUB patients. Therefore, TCM therapy can provide an alternative option for these patients. TCM therapy has advantages in treating the patients with gynaecological disorders, including DUB, premenstrual syndrome, menopausal syndrome, and uterine fibroids [8, 9]. DUB is known as “flooding and spotting (Ben Lou)” in TCM literature. In TCM theory, normal menstrual cycle and fertility are regulated by the thoroughfare and controlling vessels (Chong Ren) and the essential qi of kidney. Strengthening the thoroughfare vessels, supplementing the kidney yin and yang, dissipating blood stasis, and cooling the blood to secure controlling vessels are the main principles in TCM treatments of DUB. However, a large-scale survey on the complementary TCM utilization among patients of DUB is lacking.

Therefore, this study intends to investigate TCM usage and prescription patterns for patients with DUB. We aimed to investigate the core prescription of TCM for patients with DUB and provide valuable information for TCM doctors and gynecologists. The results of this

study will be useful for further research in clinical trials and pharmacological investigations in the future.

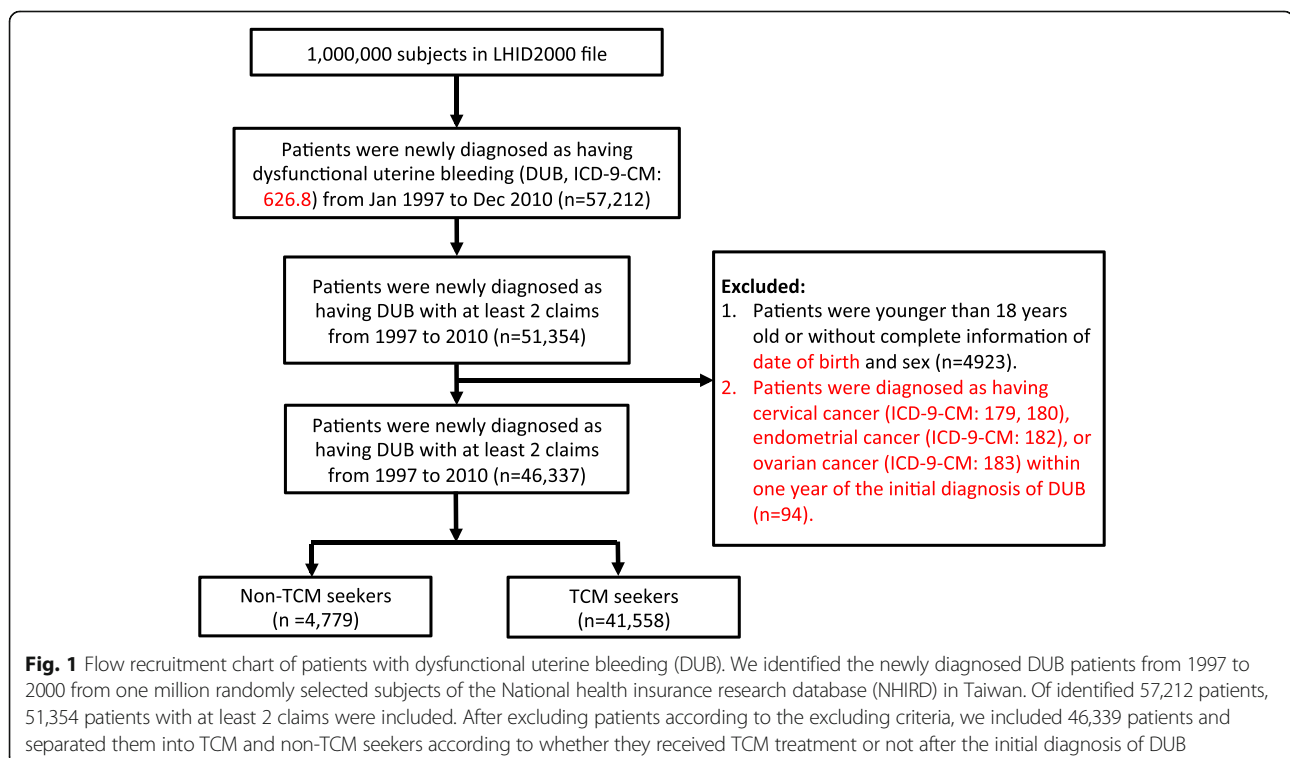
## Methods

### Data sources

The National Health Insurance (NHI) program was launched in Taiwan in 1995. It has covered more than 99% of Taiwanese residents in 2015 [10]. TCM services, including Chinese herbal medicines, acupuncture/moxibustion, and Chinese traumatology therapy, have been covered by the NHI program since 1996. The NHI administration constructed a National Health Insurance Research Database (NHIRD), which was managed by the National Health Research Institutes in Taiwan. All of the datasets were de-identified and encrypted before release for scientific research. This database contains original data including demographic characteristics, medical care facilities, outpatient and inpatient visits, visit dates, diagnostic codes, management, prescriptions and medical expenditures. The diagnostic codes were in the format of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

### Study population

A randomly selected sample with one million individuals who were enrolled in the NHI program was analyzed. Patients with newly diagnosed DUB (ICD-9-CM codes 626.8) from January 1, 1997 to December 31, 2010 were identified from the database (Fig. 1). To avoid the inclusion of patients who did not truly have DUB, we only included the



patients with at least 2 claims of DUB. We excluded the patients who were less than 18 years of age, or were missing information on their sex (male and female) and date of birth. Moreover, we excluded patients who were diagnosed as having cervical cancer, endometrial cancer, or ovary cancer within one year of the initial diagnosis of DUB. TCM seekers were defined as those who visited the TCM doctors after they were diagnosed as having DUB. Non-TCM seekers were defined as patients who never visited TCM clinics after the initial diagnosis of DUB. Ultimately, 46,337 subjects were included and were divided into groups of TCM seekers ( $n = 41,558$ ) and non-TCM seekers ( $n = 4779$ ). This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115).

### Traditional Chinese medicine treatments

Chinese herbal formulas were listed in pin-yin name and English name. Single herbs were listed in pin-yin name, Chinese materia medica name and plant name. The TCM indications of the Chinese herbal formulas and single herbs were based on TCM theory [11, 12]. Full botanical names comply with the International Plant Names List (IPNI; <http://www.ipni.org>) and The Plant List (<http://www.theplantlist.org/>) [13]. We used a network analysis open-sourced freeware NodeXL (<http://nodexl.codeplex.com/>) to determine the core pattern of Chinese herbal medicine prescribed for DUB patients. As described in our previous reports [14], the thicker the line was, the more interrelated were the Chinese herbal formulas and the co-prescribed Chinese herbal formulas.

We analyzed the acupuncture and Chinese traumatology that patients received by the treatment codes in the datasets. Acupuncture includes traditional Chinese manual acupuncture, electroacupuncture, and moxibustion. Chinese traumatology indicates traditional Chinese medicine traumatology and orthopedics, which is a combination of massage, acupressure, and body manipulation.

### Statistical analysis

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.). A univariate analysis was conducted to compare the TCM seekers with the non-TCM seekers. The data analysis included descriptive statistics, including the frequency of TCM prescriptions, the patients' demographic characteristics, indications for the prescription of TCM, and the most frequently prescribed herbal formulas and herbs for the treatment of DUB. We used t-test and chi-square test to examine the differences of numerical variables and categorical variables between two cohorts, respectively. The frequency of co-morbidities, which were the medical conditions as the reasons that DUB patients visited the clinics, between the two cohorts was compared using chi-square

test. A  $P$ -value of  $<0.05$  was considered statistically significant. The urbanized residence levels of all individuals were classified into four grades based on a previous study. Level 1 represents the highest urbanized level and 4 represents the lowest level [15].

### Results

Among one million beneficiaries, a total of 46,339 patients with newly diagnosed DUB between 1997 and 2010 were enrolled in this study (Fig. 1). Among these subjects, 89.69% ( $n = 41,558$ ) visited TCM doctors for clinical consultation or treatment. Patients within the range of 18–29 years old were most likely to receive TCM treatment (Table 1). Patients who lived in highly urbanized areas preferred to use TCM. Large portion of TCM seekers also took Western medications, especially tranexamic acid and NSAIDs.

With regard to the treatment approaches, 55.41% of the TCM seekers received combined treatment of both Chinese herbal remedies and acupuncture/traumatology, and 44.28% of patients only received prescribed Chinese herbal remedies (Table 2). Regarding the frequency of visits, 71.02% of patients visited TCM clinics for 1 to 3 times/year, while 18.48% of patients consulted TCM doctors more than 6 times/year.

We compared the frequency of different diseases, included DUB-related and unrelated co-morbidities, between non-TCM and TCM seekers (Table 3). TCM seekers had high frequency of anemia, menopausal syndrome, and female infertility. Moreover, TCM seekers also had higher frequency in psychological symptoms such as depression, insomnia, or sleep disturbance. High incidence of vertigo/dizziness, migraine/headache, digestive disorders, and upper respiratory infection in TCM seekers were also demonstrated.

To identify the prescription patterns, we further analyzed the Chinese herbal formulas prescribed by TCM doctors. The most commonly used TCM formula and single herb were Jia-Wei-Xiao-Yao-San (Bupleurum and Peony Formula) and Yi-Mu-Cao (Herba Leonuri), respectively (Table 4 and Table 5). The core patterns of Chinese formulas and herbs prescribed for DUB patients were examined in the network analysis. The core pattern and the most frequently used combinations of formulas and single herbs consisted of Jia-Wei-Xiao-Yao-San, Xiang-Fu (Rhizoma Cyperi), and Yi-Mu-Cao (Herba Leonuri) (Fig. 2).

### Discussions

In this study, we found that more than 90% of patients with DUB received TCM treatment. Patients with young age (18–29 y/o) or patients lived in highly urbanized areas were more likely to receive TCM treatment. Of the TCM seekers in our study, more than half of them received both herbal medicine and acupuncture/traumatology. Jia-Wei-

**Table 1** Demographic characteristics of the patients with newly diagnosed dysfunctional uterine bleeding from 1997 to 2010 in Taiwan

Variable	non-TCM seekers		TCM seekers		p value <sup>§</sup>
	n = 4779 (10.31%)		n = 41,558 (89.69%)		
	n	%	n	%	
Age at baseline					<.0001
18–29	1813	37.94	19,241	46.3	
30–39	1424	29.8	12,032	28.95	
≥ 40	1542	32.27	10,285	24.75	
Mean (SD)	34.84(10.42)		32.59(9.58)		<.0001 <sup>‡</sup>
Urbanization levels					0.0042
1 (highest)	1554	32.54	12,975	31.23	
2	1509	31.6	12,944	31.16	
3	780	16.33	7656	18.43	
4+ (lowest)	933	19.54	7966	19.18	
Conventional drug use					
Progesterone <sup>a</sup>	2475	51.79	26,681	64.2	<.0001
Estrogen	2291	47.94	24,531	59.03	<.0001
Combined oral contraceptives	364	7.62	4752	11.43	<.0001
Danazol	45	0.94	766	1.84	<.0001
GnRH agonists	2	0.04	18	0.04	0.99 <sup>§</sup>
Tranexamic acid	2861	97.51	41,335	99.51	<.0001
NSAIDs	4660	97.51	41,355	99.51	<.0001
Surgery in the follow-up period <sup>b</sup>					0.0184
No	4230	88.51	36,288	87.32	
Yes	549	11.49	5270	12.68	

<sup>‡</sup>t test; <sup>§</sup>Chi-square; <sup>§</sup>Fisher exact test

Abbreviations: TCM traditional Chinese medicine, NSAIDs non-steroidal anti-inflammatory drugs

<sup>a</sup>Progesterone: progesterone only pills, medroxyprogesterone acetate

<sup>b</sup>Surgery: endometrial ablation, resection, and hysterectomy

Xiao-Yao-San (Bupleurum and Peony Formula) and Yi-Mu-Cao (Herba Leonuri) were the most commonly used TCM formula and single herb, respectively. This was the first population-based cohort study to investigate the TCM utilization patterns among patients with DUB. The analysis of TCM formulas in DUB treatment could provide useful information for further clinical trials and pharmacological investigations.

Our result revealed that patients with young age or lived in highly urbanized areas preferred to receive TCM treatment, which was consistent with the previous studies [16, 17]. TCM is popular among female patients. Our previous study found that patients with uterine fibroid had a high utilization rate of TCM [9]. In this study, we found that large portions of TCM seekers also received conventional treatment. It is possible that patients with better

**Table 2** Distribution of different treatment types of traditional Chinese medicine received by patients with dysfunctional uterine bleeding, stratified by the number of outpatient visits

Number of TCM visits (times/per year)	Only Chinese herbal medicine N = 18,401 (44.28%)	Only Acupuncture or traumatology N = 130 (0.31%)	Combination of both treatment N = 23,027 (55.41%)	Total of TCM seekers (N = 41,558)
	n (%)	n (%)	n (%)	n (%)
1–3	15,460 (84.02)	128 (98.46)	13,925 (60.47)	29,513 (71.02)
4–6	1255 (6.82)	0	3110 (13.51)	4367 (10.51)
>6	1689 (9.16)	2 (1.54)	5992 (26.02)	7678 (18.48)

Abbreviation: TCM traditional Chinese medicine

Acupuncture includes traditional Chinese manual acupuncture, electroacupuncture, and moxibustion. Traumatology indicates traditional Chinese medicine traumatology and orthopedics, which is a combination of massage, acupressure, and body manipulation

**Table 3** Frequency of different diseases in patients with dysfunctional uterine bleeding

Disease (ICD-9-CM)	Non-TCM seekers		TCM seekers		p value*
	Frequency	%	Frequency	%	
DUB related					
Anemia (280.9, 281.8, 285.9)	799	16.72	9583	23.06	<.0001
Menopausal syndrome (627)	746	15.61	9071	21.83	<.0001
Female infertility (628)	311	6.51	5807	13.97	<.0001
Complications of pregnancy, child birth and the puerperium (630–676)	1761	36.85	18,785	45.20	<.0001
DUB unrelated					
Vertigo, dizziness, Meniere's Syndrome (386, 780.4, 780.7)	1813	37.94	25,138	60.49	<.0001
Depression, insomnia, sleep disorders (300, 311, 307.4, 780.5)	1449	30.32	25,976	62.51	<.0001
Migraine and headache (346, 784.0)	1753	36.68	27,494	66.16	<.0001
Upper respiratory tract infection (460–465, 784.1)	4475	93.64	41,111	98.92	<.0001
Digestive disorders (536, 564, 787.7)	2557	53.50	33,740	81.19	<.0001

\*Chi-square test

Abbreviation: TCM traditional Chinese medicine, DUB dysfunctional uterine bleeding

compliance to Western medications would be more likely to use TCM or that the severity of the disease was higher in TCM seekers. Because of the concern over side effects from the conventional treatment, patients with DUB may tend to seek TCM service for a second opinion. More than half of TCM seekers received both herbal medicine and acupuncture. One of the possible reasons is that the DUB patients had more complicated situations that required a

combinational treatment of herbal remedies and acupuncture. The complicated situations of patients with DUB as revealed in Table 3 also indicated that they commonly had psychological disorders, anemia, migraine or other systemic disorders.

Of the top ten commonly prescribed formulas identified in our study, Jia-Wei-Xiao-Yao-San and Dang-Gui-Shao-Yao-San share common features to nourish blood, regulate

**Table 4** The top ten most commonly prescribed herbs for patients with dysfunctional uterine bleeding

Pin-yin name	Chinese materia medica name	Botanical name	Indication for TCM syndrome		Frequency of prescription, times (%)	Average daily dose (g)
			DUB related	DUB unrelated		
Yi-Mu-Cao	Herba Leonuri	Leonurus heterophyllus Sweet	Menstrual irregularities due to blood stasis with edema		4341 (0.08)	6.9
Xiang-Fu	Rhizoma Cyperi	<i>Cyperus rotundus</i> L.	Irregular menstruation because of liver qi stagnation	Breast distention	2802 (0.05)	6.5
Yan-Hu-Suo	Rhizoma Corydalis	Corydalis yanhusuo W. T. Wang	Irregular menstruation because of liver qi stagnation	Pain relief	1742 (0.03)	6.6
Du-Zhong	Cortex Eucommiae Ulmoidis	Eucommia ulmoides Oliv.	Deficiency in liver and kidney	Weakness of muscles, tendons, and bones	1617 (0.03)	7.6
Xian-He-Cao	Herba Agrimoniae	<i>Agrimonia eupatoria</i> L. var. pilosa Mak		Excessive bleeding	1504 (0.03)	6.8
Dan-Shen	Radix Salviae Miltiorrhizae	Salvia miltiorrhiza Bge.	Irregular menstruation because of blood and qi stagnation	Pain relief	1477 (0.03)	7.9
Nu-Zhen-Zi	Fructus Ligustri Lucidi	<i>Ligustrum lucidum</i>	Yin deficiency in liver and kidney		1213 (0.02)	7.2
Xu-Duan	Radix Dipsaci	Dipsacus asperoides, C. Y.Chent et TM Ai	Deficiency in liver and kidney	Weakness of muscles, tendons, and bones	1191 (0.02)	7.2
Tu-Si-Zi	Semen Cuscutae Chinensis	Cuscuta chinensis Lam.	Yin deficiency in liver and kidney, infertility		1133 (0.02)	7.0
Chuan-Lian-Zi	Fructus Meliae Toosendan	<i>Melia azedarach</i> L. sub. Var. Toosendan Makino	Liver qi stagnation	Pain relief	1028 (0.02)	6.7

Abbreviation: TCM traditional Chinese medicine, DUB dysfunctional uterine bleeding

Frequency; the used times of the specific herb; %: the used times of the specific herb over the used times of all herbs for DUB patients

**Table 5** The top ten most commonly prescribed formulas for patients with dysfunctional uterine bleeding

Pin-yin name	English name	Constitutions		Indication for TCM syndrome		Frequency of prescription, times (%)	Average daily dose (g)
		Pin-yin name	Chinese material medica name	Botanical name	DUB related		
Jia-Wei-Xiao-Yao-San	Bupleurum and Peony Formula	Dang-Gui	Radix Angelicae Sinensis	Angelica sinensis (Oliv.) Diels	Irregular menstruation because of spleen qi deficiency and liver blood deficiency with heat, liver qi stagnation	Irritability, abdominal pain, depression	7654 (0.14)
		Fu-Ling	Poria,	Poria cocos (Schw.) Wolf			
		Zhi-Zi	Fructus Gardeniae	<i>Gardenia jasminoides</i> J.Ellis			
		Bo-He	Herba Menthae Haplocalycis	Mentha haplocalyx Briq.Field			
		Bai-Shao	Radix Paeoniae Alba	<i>Paeonia lactiflora</i> Pall			
		Chai-Hu	Radix Bupleuri	Bupleurum chinense DC.			
		Gan-Cao	Radix Glycyrrhizae	Glycyrrhiza uralensis Fisch			
		Bai-Zhu	Rhizoma Atractylodis Macrocephalae	Atractylis macrocephala Koidz			
		Mu-Dan-Pi	Cortex Moutan Radicis	<i>Paeonia suffruticosa</i> Andr.			
		Wei-Jiang	Rhizoma Zingiberis officinales	<i>Zingiber officinale</i> Rosc.			
Dang-Gui-Shao-Yao-San	Dang Gui and Peony Powder	Dang-Gui	Radix Angelicae Sinensis	Angelica sinensis (Oliv.) Diels	Liver blood deficiency	Abdominal pain, dizziness, edema with inhibited urination	3147 (0.06)
		Fu-Ling	Poria	Poria cocos (Schw.) Wolf			
		Bai-Shao	Radix Paeoniae Alba	Paeonia lactiflora Pall.			
		Bai-Zhu	Rhizoma Atractylodis Macrocephalae	Atractylodes macrocephala Koidz			
		Chuan-Xiong	Rhizoma Chuanxiong	Ligusticum chuanxiong Hort.			
		Ze-Xie	Rhizoma Alismatis	<i>Alisma plantago-aquatica</i> L.			
		Gui-Zhi	Ramulus Cinnamomi Cassiae	<i>Cinnamomum cassia</i> Blume			
		Fu-Ling	Poria	Poria cocos (Schw.) Wolf			
		Mu-Dan-Pi	Cortex Moutan Radicis	<i>Paeonia suffruticosa</i> Andr.			
		Chi-Shao		<i>Paeonia lactiflora</i> Pall.			
Gui-Zhi-Fu-Ling-Wan	Cinnamon and Poria Pills	Gui-Zhi	Ramulus Cinnamomi Cassiae	<i>Cinnamomum cassia</i> Blume	Blood stasis in pelvic cavity	Lower abdominal pain	2841 (0.05)
		Fu-Ling	Poria	Poria cocos (Schw.) Wolf			

**Table 5** The top ten most commonly prescribed formulas for patients with dysfunctional uterine bleeding (Continued)

Formula	Indication	Herbs	Frequency	OR	95% CI	
Wen-ling-Tang	Flow warming decoction	Tao-Ren	Radix Paeoniae Lactiflorae			
		Wu-Zhu-Yu	Semen Persicae	<i>Prunus persica</i> (L.) Batsch.		
		Gui-Zhi	Fructus Evodiae Rutaecarpae	<i>Evodia rutaecarpa</i> (Juss.) Benth.	2345 (0.04)	6.7
		Dang-Gui	Ramulus Cinnamomi Cassiae	<i>Cinnamomum cassia</i> Blume		
		Chuan-Xiong	Radix Angelicae Sinensis	<i>Angelica sinensis</i> (Oliv.) Diels		
		Bai-Shao	Radix Chuanxiong	<i>Ligusticum chuanxiong</i> Hort.		
		E-Jiao	Radix Paeoniae Alba	<i>Paeonia lactiflora</i> Pall.		
		Mai-Men-Dong	Colla Corii Asini	<i>Equus asinus</i> L.		
		Mu-Dan-Pi	Tuber Ophiopogonis Japonici	<i>Ophiopogon japonicas</i> (Thunb.) Ker_Gawl		
		Ren-Shen	Cortex Moutan Radicis	<i>Paeonia suffruticosa</i> Andr.		
Xiong-Guei-Jiao-Ai-Tang	Decoction of Donkey-Skin Glue and Artemisia	Gan-Cao	Radix Ginseng	<i>Panax ginseng</i> C. A. Mey		
		Sheng-Jiang	Radix Glycyrrhizae	<i>Glycyrrhiza uralensis</i> Fisch		
		Ban-Xia	Rhizoma Zingiberis officinales	<i>Zingiber officinale</i> Rosc.		
		Chuan-Xiong	Rhizoma Pinelliae Ternatae	<i>Pinellia ternate</i> (Thunb.) Breit		
		Dang-Gui	Chuanxiong	<i>Ligusticum chuanxiong</i> Hort.		
		E-Jiao	Radix Angelicae Sinensis	<i>Angelica sinensis</i> (Oliv.) Diels		
		Gan-Cao	Colla Corii Asini	<i>Equus asinus</i> L.		
		Shu-Di-Huang	Radix Glycyrrhizae	<i>Glycyrrhiza uralensis</i> Fisch		
		Bai-Shao	Radix Rehmanniae	<i>Rehmannia glutinosa</i> Libosch		
		Al-Ye	Radix Paeoniae Alba	<i>Paeonia lactiflora</i> Pall		
	Folium Artemisiae Argyi	<i>Artemisia argyi</i> Levl. et Vant.				
			Prevents miscarriage	3147 (0.06)	6.4	
			Blood deficiency			
			Blood stasis			

**Table 5** The top ten most commonly prescribed formulas for patients with dysfunctional uterine bleeding (Continued)

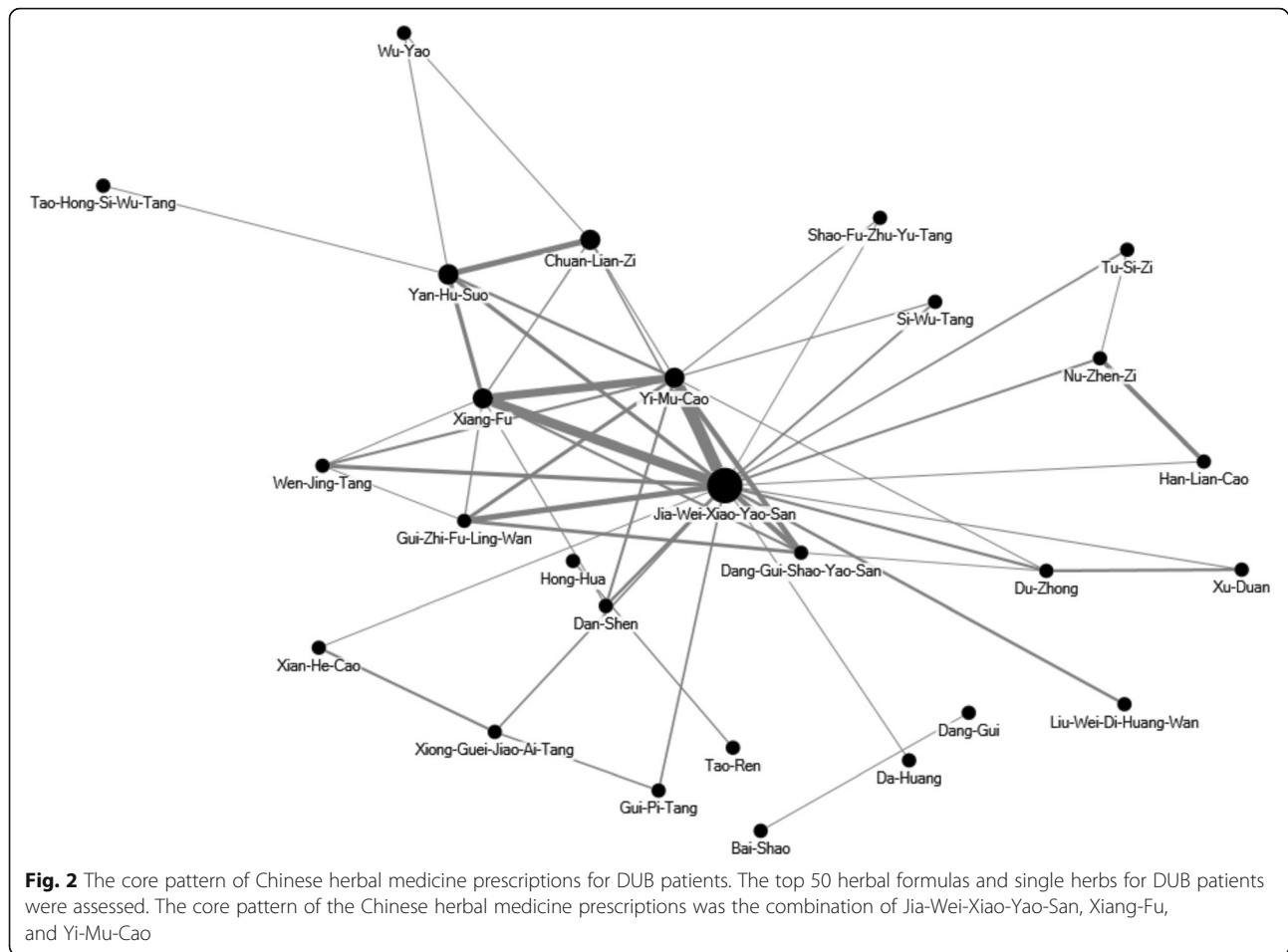
Gui-Pi-Tang	Restore the Spleen Decoction	Ren-Shen Long-Yan-Rou Huang-Qi Gan-Cao Bai-Zhu Fu-Ling Mu-Xiang Dang-Gui	Radix Ginseng Aristolis Euphorbiae Longanae Radix Astragali Radix Glycyrrhizae Rhizoma Atractylodis Macrocephalae Poria Radix Aucklandiae Radix Angelicae Sinensis	Panax ginseng C. A. Mey Dimocarpus longans Lour. Astragalus henryi Oliv. Glycyrrhiza uralensis Fisch Atractylis macrocephala Koidz Poria cocos (Schw.) Wolf Aucklandia lappa DC. Angelica sinensis (Oliv.) Diels	Blood deficiency, vaginal spotting because of qi deficiency	1812 (0.03)	6.7
Si-Wu-Tang	Four Substances Decoction	Suan-Zao-Ran Yuan-Zhi Sheng-Jiang Da-Zao	Semen Zizyphi Spinosae Radix Polygalae Tenuifoliae Radix Zingiberis officinalis Fructus Zizyphi Jujube	Ziziphus jujube var. Spinosa (Bunge) Hu ex H. F. Chow Polygala tenuifolia Willd. Zingiber officinale Rosc. Ziziphus jujuba Mill.		1554 (0.03)	6.9
Bu-Zhong-Yi-Qi-Tang	Tonify the Middle and Augment the Qi Decoction	Bai-Shao Dang-Gui Chuan-Xiong Huang-Qi Ran-Shen Bai-Zhu Gan-Cao Dang-Gui Chen-Pi Sheng-Ma	Radix Paeoniae Alba Radix Angelicae Sinensis Rhizoma Chuanxiong Radix Astragali Radix Ginseng Rhizoma Atractylodis Macrocephalae Radix Glycyrrhizae Radix Angelicae Sinensis Pericarpium Citri Reticulatae Radix Cirmicifugae	Paeonia lactiflora Pall Angelica sinensis (Oliv.) Diels Ligusticum chuanxiong Hort. Astragalus henryi Oliv. Panax ginseng C. A. Mey Atractylis macrocephala Koidz Glycyrrhiza uralensis Fisch Angelica sinensis (Oliv.) Diels Citrus reticulata Blanco Cirmicifuga foetida, L. var., intermedia, Regel	Vaginal spotting because of qi deficiency Weakness because of qi deficiency	1317 (0.02)	6.7



**Table 5** The top ten most commonly prescribed formulas for patients with dysfunctional uterine bleeding (Continued)

Liu-Wei-Di-Huang-Wan	Six Ingredient Pill with Rehmannia	Chai-Hu Shu-Di-Huang Shan-Zhu-Yu Shan-Yao Fu-Ling Mu-Dan-Pi Ze-Xie Xiao-Hui-Xiang Pao-Jiang Yan-Hu-Suo Dang-Gui Chuan-Xiong Mo-Yao Rou-Gui Chi-Shao Pu-Huang Wu-Ling-Zhi	Radix Bupleuri Radix Rehmanniae Fructus corni officinalis Radix Dioscoreae Oppositae Poria Cortex Moutan Radicis Rhizoma Alismatis Fructus Foeniculi Vulgaris Rhizoma Zingiberis officinales Rhizoma Corydalis Radix Angelicae Sinensis Rhizoma Chuanxiong Myrrh Ramulus Cinnamomi Cassiae Radix Paeoniae Lactiflorae Pollen Typhae excrementum Trogloteri Xanthipes	Bupleurum chinense DC. Rehmannia glutinosa Libosch <i>Cornus officinalis</i> Sieb. et Zucc. Dioscorea opposita Thunb. Poria cocos (Schw.) Wolf Paeonia suffruticosa Andr. Alisma orientale (Sam.) Juzep. <i>Foeniculum vulgare</i> Mill. Zingiber officinale Rosc. Corydalis yanhusuo W. T. Wang Angelica sinensis (Oliv.) Diels Ligusticum chuanxiong Hort. Commiphora molmol, Engi. Cinnamomum cassia Blume Paeonia lactiflora Pall. <i>Typha angustifolia</i> L. <i>Trogloteris xanthipes</i> Milne-Edwards	Deficiency in liver and kidney	1286 (0.02)	7.2
Shao-Fu-Zhu-Yu-Tang	Drive Out Stasis from the Lower Abdomen Decoction	Xiao-Hui-Xiang Pao-Jiang Yan-Hu-Suo Dang-Gui Chuan-Xiong Mo-Yao Rou-Gui Chi-Shao Pu-Huang Wu-Ling-Zhi	Fructus Foeniculi Vulgaris Rhizoma Zingiberis officinales Rhizoma Corydalis Radix Angelicae Sinensis Rhizoma Chuanxiong Myrrh Ramulus Cinnamomi Cassiae Radix Paeoniae Lactiflorae Pollen Typhae excrementum Trogloteri Xanthipes	Alisma orientale (Sam.) Juzep. <i>Foeniculum vulgare</i> Mill. Zingiber officinale Rosc. Corydalis yanhusuo W. T. Wang Angelica sinensis (Oliv.) Diels Ligusticum chuanxiong Hort. Commiphora molmol, Engi. Cinnamomum cassia Blume Paeonia lactiflora Pall. <i>Typha angustifolia</i> L. <i>Trogloteris xanthipes</i> Milne-Edwards	Blood stasis and qi stagnation	1030 (0.02)	7.8

Abbreviation: TCM traditional Chinese medicine, DUB dysfunctional uterine bleeding  
Frequency indicates the used times of the specific herbal formula, and % indicates the used times of the specific herbal formula over the used times of all herbal formulas for DUB patients



menstrual cycle, and relieve emotional and psychological symptoms clinically. Previous studies found that Jia-Wei-Xiao-Yao-San ameliorated depression in menopausal women through increasing serum TNF- $\alpha$  [18, 19] and Dang-Gui-Shao-Yao-San improved depression-like behaviors in murine model through decreasing central arginine vasopressin [20]. Highly utilization rate of these two formulas may be due to the high incidence of psychological disorders in patients with DUB. Moreover, Dang-Gui-Xiao-Yao-San also exerted analgesic effect on dysmenorrhea through suppression of uterine smooth muscle contractions [21] and corrected luteal phase insufficiency [22]. Gui-Zhi-Fu-Ling-Wan, the formula commonly used to treat menstrual disorders caused by blood stasis, has been demonstrated to exert estrogen-like activity to relieve the symptoms of climacteric disorders [23] and decrease uterine contraction to attenuate dysmenorrhea [24].

Of the ten commonly used single herbs identified in this study, Yan-Hu-Suo (Rhizoma Corydalis) and Xiang-Fu (Rhizoma Cyperi) are traditionally used to treat qi stagnation to relieve pain. Moreover, Yan-Hu-Suo has been used to promote blood circulation, alleviate amenorrhea and dysmenorrhea, and treat puerperal blood stasis [25].

Tetrahydroprotoberberines (THPBs), isolated from Yan-Hu-Suo, was demonstrated to suppress D2 dopamine receptors in the central nervous system to exert analgesic effect [26]. A previous study revealed that Xiang-Fu has estrogen-like and neuroprotective effects in estrogen-deprived mice [27]. The other commonly used herbs in this study, Yi-Mu-Cao (Herba Leonuri) and Dan-Shen (Radix Salviae Miltiorrhizae), were also usually used for the treatment of patients with uterine fibroid [9]. Previous studies demonstrated that leonurine, an alkaloid present in Yi-Mu-Cao, had anti-fibrotic [28], anti-diabetic [29], anti-atherosclerotic [30], and heart protective effects [31] in murine models. Dan-Shen has been demonstrated to enhance the estrogenic effects in ovariectomized rats [32] and stimulate estrogen receptor to exert the effects of oxidative stress [33], anti-inflammation [34] and anti-cancer [35]. Anti-depressive effect of Danshen has been also demonstrated in a rat model [36].

The core pattern of Chinese herbal medicine for DUB patients was the combination of Jia-Wei-Xiao-Yao-San, Xiang-Fu, and Yi-Mu-Cao, which was also the most commonly used combination for premenstrual syndrome [37]. There is no mechanistic study or clinical trials to evaluate

the efficacy of this combination. In clinical application according to TCM theory, Jia-Wei-Xiao-Yao-San was developed to treat spleen qi deficiency and liver blood deficiency with heat. Xiang-Fu is used to treat qi stagnation, and Yi-Mu-Cao is used to treat blood stasis. In TCM theory, the combination of Jia-Wei-Xiao-Yao-San, Xiang-Fu, and Yi-Mu-Cao are usually used to supply qi in spleen, supply blood and clean heat in liver, and treat qi stagnation and blood stasis to regulate menstruation. The potential therapeutic efficacy and mechanisms of this combination merit more clinical trials and mechanistic studies.

There are some limitations in our study. The laboratory data and the imaging findings were not available in this database. The differences in disease severity between the TCM seekers and the non-TCM seekers cannot be evaluated. We could only identify the patients who received the conventional drug treatment and surgery in TCM seekers and non-TCM seekers. It has to be noted that DUB requires exclusion diagnostic procedure after clinical and laboratory examination. In the NHIRD datasets, we could identify the specific codes for the laboratory examinations, sonography, and pelvic examination in the datasets. Although we only included those who had at least 2 claims as the DUB patients and further excluded those who were diagnosed as having cervical cancer, endometrial cancer, or ovary cancer within one year of the initial diagnosis of DUB to avoid the selection bias; however, the results of these examinations were not revealed in the datasets. It is also likely that without proper exclusion diagnostic procedures such as clinical and laboratory examination, the number of DUB patients may be exaggerated.

Moreover, herbs purchased at patients' own expense beyond the NHI programs were not included in this study since the NHI program only reimburses Chinese herbal medicines manufactured by good manufacturing practice (GMP) -certified pharmaceutical companies in Taiwan. However, because the cost of Chinese herbal products reimbursed by the NHI program is much less than the herbs in the market, the likelihood of purchasing herbs outside of the NHI program is relatively low. In addition, progestin intrauterine device was not reimbursed by the National Health Insurance program until 2015, so we could not identify the patients who used progestin intrauterine device in our study. The other limitation of this study is that the direct efficacy of TCM treatment cannot be evaluated. The compliance to prescriptions was not revealed in the database. These factors should be evaluated in the high-quality, randomized, controlled clinical trials in the future.

## Conclusions

This is the first large-scale population-based study on complementary TCM utilization in patients with DUB.

We found that the utilization rate of complementary TCM among patients with DUB is high. The prescription patterns identified in this study could be useful for future clinical studies or pharmacological investigations. Future high-quality, randomized, controlled clinical trials combined with laboratory data may help to determine the efficacy of TCM for DUB patients.

## Abbreviations

DUB: Dysfunctional uterine bleeding; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; NHI: National Health Insurance; NHIRD: National Health Insurance Research Database; NSAIDs: Non-steroidal anti-inflammatory drugs; TCM: Traditional Chinese medicine

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## Availability of data and materials

The datasets we analyzed from NHIRD was provided by the National Health Insurance Administration and maintained by the National Health Research Institutes of Taiwan. The use of NHIRD is limited to research purposes only. Applicants must follow the Computer-Processed Personal Data Protection Law (<http://www.winklerpartners.com/?p=987>) and related regulations of National Health Insurance Administration and National Health Research Institutes.

## Authors' contributions

HRY and STY contributed equally. YRL and HRY conceptualized the study. JHC performed the statistical analysis. YRL, MYW, HRY, and STY contributed to the interpretation of the TCM data and pharmacological mechanisms. YRL and STY contributed to the interpretation of the western medicine data. YRL and MYW drafted the manuscript. HRY and STY finalized the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115) and also the National Health Research Institute, the data holder of the NHI database. The patient consent was exempted for the total anonymity of all research data in this study.

## Consent for publication

Not applicable in this section.

## Competing interests

The authors declare that they have no competing interests.

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**Author details**

<sup>1</sup>Graduate Institute of Chinese Medicine, School of Chinese Medicine, College of Chinese Medicine, China Medical University, 91 Hsueh-Shih Rd. North District, Taichung 404, Taiwan. <sup>2</sup>Department of Chinese Medicine, China Medical University Hospital, 2 Yude Rd, North District, Taichung 404, Taiwan. <sup>3</sup>Management Office for Health Data, China Medical University Hospital, 2 Yude Rd, North District, Taichung 404, Taiwan. <sup>4</sup>College of Medicine, China Medical University, Taichung 404, Taiwan. <sup>5</sup>Research Center for Chinese Herbal Medicine, China Medical University, Taichung 404, Taiwan. <sup>6</sup>Department of Biotechnology, Asia University, Taichung 41354, Taiwan. <sup>7</sup>Research Center for Traditional Chinese Medicine, Department of Medical Research, China Medical University Hospital, 2 Yude Rd, North District, Taichung 404, Taiwan. <sup>8</sup>Department of Radiology, China Medical University Hospital, 2 Yude Rd, North District, Taichung 404, Taiwan.

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