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Original Article

Core prescription pattern of Chinese herbal medicine for depressive disorders in Taiwan: a nationwide population-based study

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ABSTRACT

Background: Depressive disorders (DD) affect not only mood and behavior but also various physical functions. Traditional Chinese medicine (TCM) has been shown to have some benefits in treating DD. However, one formula or one single herb might be not show high efficacy when used to treat depression. Thus, this study aimed to examine the core prescription pattern of Chinese herbal medicine (CHM) among patients with DD in Taiwan as a reference for related research and clinical applications.

Methods: All patients, who had been diagnosed with major depressive disorder or minor depression or dysthymia without any other baseline diseases and had at least one CHM outpatient clinical visit from 2002 to 2011, were extracted from three randomly sampled cohorts, namely the 2000, 2005 and 2010 cohorts of the National Health Insurance Research Database (NHIRD) of Taiwan. The collected data was analyzed to explore the patterns of herbal products.

Results: There were 197,146 patients with a diagnosis of DD and of these 1806 subjects had only a diagnosis of DD and utilized CHM. The most common formula was *Gan-Mai-Da-Zao-Tang* (12.19%), while *Suan-Zao-Ren* (3.99%) was the most commonly prescribed single herb. The core pattern of prescriptions consisted of a combination of *Gan-Mai-Da-Zao-Tang, Jia-Wei-Xiao-Yao-San, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang, He-Huan-Pi, Yuan-Zhi* and *Shi-Chang-Pu*.

Conclusions: This study describes the CHM core prescription pattern used to treat patients in Taiwan with DD and it is a potential candidate for study in future pharmacological or clinical trials targeting DD.

1. Introduction

According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), depressive disorders (DD) include several mood disorders (major depressive disorder, dysthymia, and so on) that not only affect emotions (anxiety, sadness), mind (slow thinking, indecisiveness) and behaviors (irritability, suicide attempts), but also affect various bodily functions (eating changes, sleeping problems) and causes disability (social isolation, trouble with interpersonal relationship).[1] As reported by Global Burden Disease study in 2016, DD were ranked among top ten leading causes of years lived with disability in Taiwan.[2] Many studies have shown that patients with DD have a relatively poor quality of life, have increased medical use, and are at risk of suicide.[3] Moreover, when DD are associated with chronic diseases, such as hypertension, diabetes, heart diseases, cancer, and so on, there are higher rates of morbidity and mortality compared to similar patients without DD.[4]

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Many studies are been carried with the aim of discovering the underlying mechanisms behind DD. Until the present it has been suggested that several related factors are involved such as monoaminergic systems, brain-derived neurotrophic factor (BDNF), the hypothalamic-pituitary-adrenal axis, and neuroinflammation.[5] The treatment of DD is based on the use of antidepressants and/or various psychological treatments. Antidepressants are effective when treating moderate and severe depression, although they are not recommended as a first line of treatment for either mild depression in adults or depression in adolescents. However, many of the side effects of antidepressants, including nausea, headache, insomnia, anxiety, weight gain, sexual dysfunction and so on, often make patients reluctant to continue to use them.[6] On the other hand, the use of psychological treatments is limited by factors such as time-consuming process, high cost (in many countries, the fee of psychological treatments is not covered by insurance), and lack of professionals (psychiatrists, psychologists, and so on).[7]

Because of the reasons mentioned above, patients with DD have looked for other treatments. In Taiwan, because Traditional Chinese Medicine (TCM) has been incorporated into health insurance system, many people use TCM to promote their health or to treat various diseases.[8,9] A study has shown that more than 40% of depression patients in Taiwan used TCM in 2003, and that younger age individuals, women, individuals with other chronic diseases, and individuals with less exposure to psychiatric treatment are likely to use TCM frequently.[10]

Chinese herbal medicine (CHM) has been demonstrated to show benefits when used to treat depression. To investigate the effects, safety, and types of CHM for depression, Yeung and his collaborators conducted a meta-analysis. This showed that three most common formulae used in clinical trials were *Xiao-Yao-Tang* or its modifications, *Chai-Hu-Shu-Gan-Tang* and *Gan-Mai-Da-Zao-Tang*; and CHM had a better efficacy than the placebo control group. The effects were equal to those of antidepressants, and, furthermore, the integration of CHM and antidepressants resulted fewer side effects when treating depressive disorders.[11] However, due to the low methodological quality of most the included studies, more randomized and better controlled trials using internationally accepted methods and standards are required to confirm the benefits of CHM for the treatment of DD.

As mentioned above, DD has been suggested to develop via a number of different possible mechanisms. One formula or one single herb might be not able to regulate all the pathways relevant to depression. Thus, it is necessary to examine if combination of different formulae or single herbs are able to enhance the treatment's effectiveness. In 1995 Taiwan established its National Health Insurance program, and 99.9% of Taiwan's population were enrolled in the system by the end of 2014. National Health Insurance Research Database (NHIRD) provides a platform for understanding the core pattern of prescribed CHM among the depressed patient population in Taiwan. Therefore, the purpose of this study was to analyze three randomly extracted cohort samples from the NHIRD database in order to investigate the core pattern of CHM prescriptions for patients with DD in Taiwan; this can then be used as a reference for related research and for specific clinical applications.

2. Methods

2.1. Data sources

NHIRD is a nationwide population-based claims database with long-term follow-up. Annually, data has been collected from National Health Insurance program and de-identified before being sent to the National Health Research Institutes to form NHIRD. The NHIRD's data includes patients' gender, age, dates of clinical visits, major disease diagnosis codes according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) format, and details of any prescription provided to the patient. All identity information of the beneficiaries and the medical facilities used are encoded in order to protect the patients' and hospitals' privacy. This study used a retrospective observational population-based design to analyze three random cohort samples from the Longitudinal Health Insurance Database (LHID2000, LHID2005, and LHID2010) to survey the patterns of prescribed CHM among patients with only a diagnosis of depressive disorder between January 1, 2002 and December 31, 2011. LHID 2000, LHID2005, and LHID2010 are three datasets which include one million beneficiaries randomly extracted from NHIRD in 2000, 2005, and 2010, respectively. The random sampling method is to assign all people in the insured population to serial numbers, and use a random number generator to generate at least one million random values, after that take the same serial numbers as one million random values to randomly select the required sample. There are no differences in demographic factors between the randomly selected sample and the entire datasets; thus, these samples could be regarded as representative of the general population. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB-2018–03–010CC).

2.2. Study subjects

The flowchart of subject extraction from the 3 million random samples forming the Taiwan NHIRDs is presented in Fig. 1. First, all patients diagnosed with major depressive disorder (ICD-9 234.2x or 234.3x), with minor depression (ICD-9 300.4) or with dysthymia (ICD-9 311) were extracted. From 2002 to 2011 in Taiwan, there were 76,425 depressed patients within LHID2000, 68,142 within LHID2005, and 52,579 within LHID2010. Second, within these DD cohorts, patients were separated into either CHM users, who had received at least one CHM prescription between 2002 to 2011 ($n = 877$ within LHID2000, $n = 859$ within LHID2005, and $n = 780$ within LHID2010, respectively), and non-CHM users, who has received no CHM prescription based on these outpatient records. Finally, only CHM users with only a diagnosis of DD were included. Claims with only one of the diagnosis codes for DD, and without any other baseline diseases, were defined as subjects with only a diagnosis of depression. The use of only a diagnosis of DD, in terms of CHM visits, should diminish measurement bias caused by CHM visits for non-depressive disorders treatments. Among the CHM users, a total of 1806 subjects (622 in LHID2000, 627 in LHIDD2005, 557 in LHID2010, respectively) achieved this criterion.

2.3. Statistical analysis

Data analysis comprised of descriptive statistics, including the basic characteristics of patients, the most common formulae used to treat DD and the most common single herbs used to treat DD. This study used SAS software, version 9.4 (SAS Institute Inc., Cary, NC, U.S.A.) to analyze the data. In addition, an open-sourced freeware NodeXL was used to discover the core pattern of CHM used when treating patients with DD, and the most frequent combinations of two formulae/single herbs were then utilized for the network analysis. Within the network, formulae and single herbs were connected via lines. The number of combinations between a certain CHM and co-prescribed CHM was used to determine the width of the line connecting them, and the thicker the width of a given line connections is used to identify important prescription patterns. For example, if CHM-A and CHM-B are more frequently co-prescribed than CHM-A and CHM-C, the width of the line between CHM-A and CHM-B will be thicker than the one between CHM-A and CHM-C. The above approach allows the core pattern

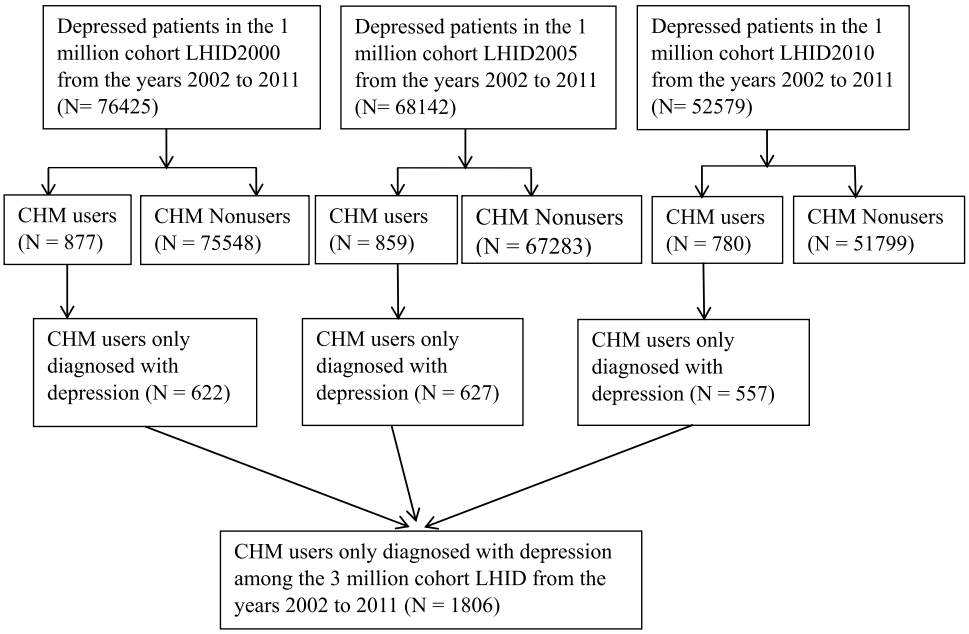

Fig. 1. Flowchart of recruitment of patients with depressive disorders from the 3 million random samples.

Table 1
Demographic characteristics of Chinese herbal medicine users among patients with depressive disorders from 2002 to 2011.

Characteristics	Chinese herbal medicine users N	%
Gender		
Male	555	30.73
Female	1251	69.27
Age		
<20	58	3.21
20–34	411	22.76
35–49	674	37.32
50–64	493	27.30
65–79	158	8.75
>=80	12	0.66
Mean±SD	44.88±14.34	
Max	88	
Min	7	
Depression diagnosis at index visit		
Major depression	254	14.06
Minor depression	622	34.44
Dysthymia	930	51.50
Number of visits for Chinese herbal products		
1–3	1306	72.31
4–6	234	12.97
>6	266	14.72
Total	1806	100

of CHM utilization to be clearly detected. This approach to identifying core prescription pattern analysis has been used in previous study.[12]

3. Results

3.1. Characteristics of DD patients

From 2002 to 2011 in Taiwan, there were 1806 subjects with only a diagnosis of DD used CHM. Table 1 presents the demographic characteristics of the CHM users. Females had a higher tendency to use CHM than males. Among the various age groups, the group with the highest percentage utilization was the 35–49 years old group (37.3%) and the mean±SD overall age was 44.88±14.34. Patients with diagnosis of dysthymia used CHM more frequently than two other groups. In addition, almost three quarters of the patients (72.3%) used CHM 1–3 times.

3.2. Top ten CHM formulae and single herbs for DD patients

The top ten CHM formulae for treating DD from 2002 to 2011 are listed in Table 2. *Gan-Mai-Da-Zao-Tang* was the most commonly prescribed formula (12.19%), with an average dose of 4.36 g, followed by *Jia-Wei-Xiao-Yao-San* (10.08%), *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang* (6.83%).

The top ten single herbs for treating DD are also listed and the most frequently used single herb is *Suan-Zao-Ren* (3.99%) with an average dose was 1.36 g (Table 3). The next common single herbs were *Da-Huang* (3.07%), *Yuan-Zhi* (2.89%).

Table 2
Ten most commonly prescribed formulae for depressive disorders (total prescription number=12,748).

Herbal formulas	Ingredients/Scientific name	Therapeutic actions	Average dose (g)	Frequency of prescription N (%)
Gan-Mai-Da-Zao-Tang	Gan-Cao (*Glycyrrhiza uralensis* Fisch), Xiao-Mai (*Triticum aestivum* L.), Da-Zao (*Ziziphus jujuba* Mill.)	Nourishes the Heart and calms the Shen	4.36	1555 (12.19%)
Jia-Wei-Xiao-Yao-San	Dang-Gui (*Angelica sinensis* (Oliv.) Diels), Bai-Shao (*Paeonia lactiflora* Pall.), Chai-Hu (*Bupleurum abchasicum* Manden.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Gan-Cao (*Glycyrrhiza uralensis* Fisch.), Mu-Dan-Pi (*Moutan officinalis* (L.) Lindl. & Paxton.), Wei-Jiang (*Zingiber officinale* Roscoe.), Bo-He (*Mentha haplocalyx* Briq.), Zhi-Zi (*Gardenia jasminoides* J.Ellis)	Courses the Liver and resolves depression	4.64	1286 (10.08%)
Chai-Hu-Jia-Long-Gu-Mu-Li-Tang	Chai-Hu (*Bupleurum abchasicum* Manden.), Sheng-Jiang (*Zingiber officinale* Roscoe), Huang-Qin (*Scutellaria baicalensis* Georgi.), Da-Zao (*Ziziphus jujuba* Mill.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Ren-Shen (*Panax ginseng* C.A.Mey), Da-Huang (*Rheum palmatum* L.), Zhi-Ban-Xia (*Pinellia ternata* (Thunb.) Makino.), Mu-Li (*Ostrea gigas* Thunb.), Gui-Zhi (*Cinnamomum cassia* Presl.), Long-Gu (*Fossilia Ossia* Mastodi)	Sedates and calms the Spirit	4.2	871 (6.83%)
Tian-Wang-Bu-Xin-Wan	Sheng-Di-Huang (*Rehmannia glutinosa* (Gaertn.) Libosch. Ex Fisch. & C.A. Mey.), Dang-Gui (*Angelica sinensis* (Oliv.) Diels), Suan-Zao-Ren (*Ziziphus jujuba* Mill.), Mai-Men-Dong (*Ophiopogon japonicus* (Thunb.) Ker Gawl.), Yuan-Zhi (*Polygala tenuifolia* Willd.). Tian-Men-Dong (*Asparagus cochinchinensis* (Lour.) Merr.), Bai-Zi-Ren (*Platycladus orientalis* (L.) Franco.), Wu-Wei-Zi (*Schisandra chinensis* (Turcz.) Baill.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Jie-Geng (*Platycodon grandiflorus* (Jacq.) A. DC.), Ren-Shen (*Panax ginseng* C.A.Mey), Dan-Shen (*Salvia miltiorrhiza* Bunge.), Xuan-Shen (*Scrophularia ningpoensis* Hemsl.)	Enriches Yin and calms the Shen	5.36	798 (6.26%)
Suan-Zao-Ren-Tang	Suan-Zao-Ren (*Ziziphus jujuba* Mill.Sclerotium), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Zhi-Mu (*Anemarrhena asphodeloides* Bge.), Chuan-Xiong (*Laserpitium striatum* Wall.), Gan-Cao (*Glycyrrhiza uralensis* Fisch.)	Clears heat in Liver and Heart, calms the Shen	4.12	405 (3.17%)
Wen-Dan-Tang	Zhi-Ban-Xia (*Pinellia ternata* (Thunb.) Makino.), Zhu-Ru (*Bambusa tuldoides* Munro.), Zhi-Shi (*Citrus aurantium* L.), Chen-Pi (*Citrus reticulata* Blanco.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Gan-Cao (*Glycyrrhiza uralensis* Fisch.), Sheng-Jiang (*Zingiber officinale* Roscoe.), Da-Zao (*Ziziphus jujuba* Mill.)	Regulates the Qi and transforms Phlegm	4.12	402 (3.15%)
Wu-Zhu-Yu-Tang	Wu-Zhu-Yu (*Evodia rutaecarpa* (Juss) Benth.), Ren-Shen (*Panax ginseng* C.A.Mey), Sheng-Jiang (*Zingiber officinale* Roscoe.), Da-Zao (*Ziziphus jujuba* Mill.)	Warms and tonifies the Spleen, Stomach, Liver and Kidneys and descends Rebellious Qi	3.64	307 (2.41%)
Gui-Pi-Tang	Ren-Shen (*Panax ginseng* C.A.Mey), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Suan-Zao-Ren (*Ziziphus jujuba* Mill.), Long-Yan-Rou (*Arillus Longan* (Lour.) Steud.), Huang-Qi (*Astragalus membranaceus* (Fisch) Bge), Dang-Gui (*Angelica sinensis* (Oliv.) Diels), Mu-Xiang (*Auklandia lappa* Clarke.), Zhi-Yuan-Zhi (*Polygala tenuifolia* Willd.), Gan-Cao (*Glycyrrhiza uralensis* Fisch.), Sheng-Jiang (*Zingiber officinale* Roscoe.), Da-Zao (*Ziziphus jujuba* Mill.)	Augments Qi, nourishes the Blood, strengthens the Spleen, nourishes the Heart	4.56	283 (2.22%)
Yi-Gan-San	Chao-Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Dang-Gui (*Angelica sinensis* (Oliv.) Diels), Chuan-Xiong (*Laserpitium striatum* Wall.), Gou-Teng (*Uncaria rhynchophyllia* (Miq.) Jacks.), Chai-Hu (*Bupleurum abchasicum* Manden.), Gan-Cao (*Glycyrrhiza uralensis* Fisch.)	Calms the Liver andregulates the Liver Qi and Blood	4.4	251 (1.97%)
Ban-Xia-Hou-Po-Tang	Ban-Xia (*Pinellia ternata* (Thunb.) Makino.), Hou-Po (*Magnolia officinalis* Rehder & E.H.Wilson.), Fu-Ling (*Poria cocos* (Schw.) Wolf.), Sheng-Jiang (*Zingiber officinale* Roscoe.), Zi-Su-Ye (*Perilla frutescens* (L.) Britton.)	Activates Qi, descends Rebellious Qi, eliminates Phlegm, and relieves Stagnation	5.16	199 (1.56%)

3.3. The prescription patterns between formulae and single herbs

The most common prescription patterns with regard to formula/single herb associations are shown in Table 4. The most common association of two formulae/single herbs was *Jia-Wei-Xiao-Yao-San* plus *Gan-Mai-Da-Zao-Tang*. The other identified patterns were *Gan-Mai-Da-Zao-Tang* plus *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang*, and *Gan-Mai-Da-Zao-Tang* plus *He-Huan-Pi*. Furthermore, *Long-Gu*, plus *Suan-Zao-Ren*, plus *Bai-He* was the most common association of three formulae/single herbs, followed by *Suan-Zao-Ren*, plus *Ye-Jiao-Teng*, plus *Bai-He*, and *Suan-Zao-Ren*, plus *Bai-He*, plus *Wu-Wei-Zi*.

The software NodeXL analyzed the top 100 common combinations of two formulae/single herb for patients with DD to identify the core pattern of the prescriptions, and the result was a combination of three formulae and three single herbs, *Gan-Mai-Da-Zao-Tang, Jia-Wei-Xiao-Yao-San, Chai-Hu-Jia-Long-Gu-Mu-Li-Tang, He-Huan-Pi, Yuan-Zhi* and *Shi-Chang-Pu* (Fig. 2).

4. Discussion

This study investigated the most common formulae and single herbs, as well as the core pattern of the prescriptions for patients with only a diagnosis of DD in Taiwan. As presented in Table 2, the most commonly prescribed formula for DD was *Gan-Mai-Da-Zao-Tang*. A previous study has reported that *Gan-Mai-Da-Zao-Tang* decoction was able to ameliorate depressive-like behaviors, attenuate glutamate levels, and enhance expression of N-methyl-D-aspartate receptors in the frontal cortex and hippocampus of unpredictable chronic mildly stressed rats,[13] as well as decreasing immobility times and regulating the concentration of monoamines using a forced swimming test model.[14] In other animal studies, this formula has been shown to have a sedative effect and lengthen the hexobarbital sleeping time,[15] as well as inhibiting sodium, calcium and potassium currents in neurons, in associated with a local anesthetic action using a nerve fiber model.[16] A meta-analysis found that *Gan-Mai-Da-Zao-Tang* was as efficient as antidepressants; fur-

Table 3
Ten most commonly prescribed single herbs for depressive disorders (total prescription number = 19,343).

Single herbs	Scientific name	Therapeutics Actions	Average dose (g)	Frequency of prescription N (%)
Suan-Zao-Ren	Ziziphi Spinosae Semen *Ziziphus jujuba* Mill.	Nourishes Heart Yin, tonifies Liver Blood andcalms the Spirit	1.36	772 (3.99%)
Da-Huang	Rhei Radix et Rhizoma *Rheum palmatum* L.	Clears heat and drains fire	0.64	595 (3.07%)
Yuan-Zhi	Polygalae Radix *Polygala tenuifolia* Willd.	Calms the Spirit, sedatesthe Heart	0.68	559 (2.89%)
Ye-Jiao-Teng	Polygoni Multiflori Caulis *Polygonum multiflorum* Thunb	Nourishes the Heart Yin and Blood and calms the Spirit	1.16	546 (2.82%)
Bai-He	Bulbus Lili *Lilium brownii* F.F. Br. var. colchesteri Wils	Clears the Heart and calms the Spirit	1.12	542 (2.80%)
Dan-Shen	Salviae Miltiorrhizae Radix *Salvia miltiorrhiza* Bunge.	Clears Heat and soothes irritability; nourishes theBlood and calms the Spirit	0.96	538 (2.78%)
He-Huan-Pi	Cortex Albiziae *Albizia julibrissin* sensu Baker.	Calms the Spirit and relieves constraint	1.16	525 (2.71%)
Mu-Li	Ostreae Testa *Ostrea gigas* Thunb.	Heavily settles and calms the Spirit	0.92	510 (2.63%)
Yu-Jin	Curcumae Radix *Curcuma aromatica* Salisb. *Curcuma longa* L.	Invigorates the Blood, dispels Blood Stasis, regulates Qi flow	1.04	492 (2.54%)
Fu-Shen	Scierotium Pararadicis Poriae Cocos *Poria cocos* (Schw). Wolf	Calms the Spirit	0.92	492 (2.54%)

Table 4
The most common prescription patterns for two and triple drug combinations in a single prescription of depressive disorders.

	Name			Number of prescription
Two combination				
1	*Jia-Wei-Xiao-Yao-San*	*Gan-Mai-Da-Zao-Tang*		580
2	*Gan-Mai-Da-Zao-Tang*	*Chai-Hu-Jia-Long-Gu-Mu-Li-Tang*		440
3	*Gan-Mai-Da-Zao-Tang*	*He-Huan-Pi*		307
4	*Shi-Chang-Pu*	*Yuan-Zhi*		288
5	*Bai-He*	*Suan-Zao-Ren*		272
6	*Jia-Wei-Xiao-Yao-San*	*Suan-Zao-Ren*		265
7	*Mu-Li*	*Long-Gu*		260
8	*Jia-Wei-Xiao-Yao-San*	*He-Huan-Pi*		256
9	*Ye-Jiao-Teng*	*Suan-Zao-Ren*		249
10	*Gan-Mai-Da-Zao-Tang*	*Suan-Zao-Ren*		240
Triple combination				
1	*Long-Gu*	*Suan-Zao-Ren*	*Bai-He*	166
2	*Suan-Zao-Ren*	*Ye-Jiao-Teng*	*Bai-He*	144
3	*Suan-Zao-Ren*	*Bai-He*	*Wu-Wei-Zi*	138
4	*Suan-Zao-Ren*	*Bai-Zi-Ren*	*Ye-Jiao-Teng*	132
	Fu-Shen	*Suan-Zao-Ren*	*Ye-Jiao-Teng*	132
5	*Bai-Zi-Ren*	*Ye-Jiao-Teng*	*Bai-He*	129
	Suan-Zao-Ren	*Bai-Zi-Ren*	*Bai-He*	129
6	*Fu-Shen*	*Bai-Zi-Ren*	*Ye-Jiao-Teng*	127
7	*Fu-Shen*	*Ye-Jiao-Teng*	*Bai-He*	125
	Fu-Shen	*Suan-Zao-Ren*	*Bai-Zi-Ren*	125
	Fu-Shen	*Suan-Zao-Ren*	*Bai-He*	125
8	*Yuan-Zhi*	*Bai-He*	*Shi-Chang-Pu*	124
9	*Fu-Shen*	*Bai-Zi-Ren*	*Bai-He*	123
10	*Long-Gu*	*Bai-Zi-Ren*	*Ye-Jiao-Teng*	114

thermore, when combined with antidepressants, *Gan-Mai-Da-Zao* decoction showed an increased effectiveness, as well as a reduction in side effects, both compared to antidepressants alone.[17]

The next most commonly prescribed formula was *Jia-Wei-Xiao-Yao-San*, which has been widely used in TCM to treat psychological disorders including depression, sleep disturbances, and anxiety disorder. Reportedly, *Jia-Wei-Xiao-Yao-San* has an antidepressant-like effect when animal models of depression are used via a hippocampal neurogenesis mechanism.[18] In addition, other experimental studies have identified anxiolytic,[19] antioxidant, neuroprotective,[20] anti-inflammatory effects[21] of *Jia-Wei-Xiao-Yao-San*. In clinical trial studies, the formula has been shown to effectively improve the quality of sleep in peri- menopausal and post-menopausal women,[22] to improve depression in patients with premenstrual dysphoric disorder,[23] and to reduce vasomotor and psychological symptoms in climacteric patients.[24]

The third most commonly used formula was *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang*. This formula was shown by Kazushige Mizoguchi et al. to attenuate chronic stress-induced abnormalities of the hypothalamic-pituitary-adrenal axis, which has been shown to be related to depression.[25] In another study by the same authors, the results indicated that *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang* is able to relieve chronic stress-induced depressive state via preventing dysfunction of the prefrontal cortex.[26] Additionally, this formula has been shown to decrease corticosterone levels during psychological stress and conditioned-fear stress using a mouse model. which implies that this formula could be useful when treating stress that involves emotional factors.[27]

In Taiwan, TCM physicians frequently use *Tian-Wang-Bu-Xin-Wan*, *Suan-Zao-Ren-Tang*, and *Wen-Dan-Tang* for the treatment of sleep disorders.[28] Experimental studies have suggested that *Tian-Wang-Bu-Xin-Wan* is able to promote sleeping using hyposomnia

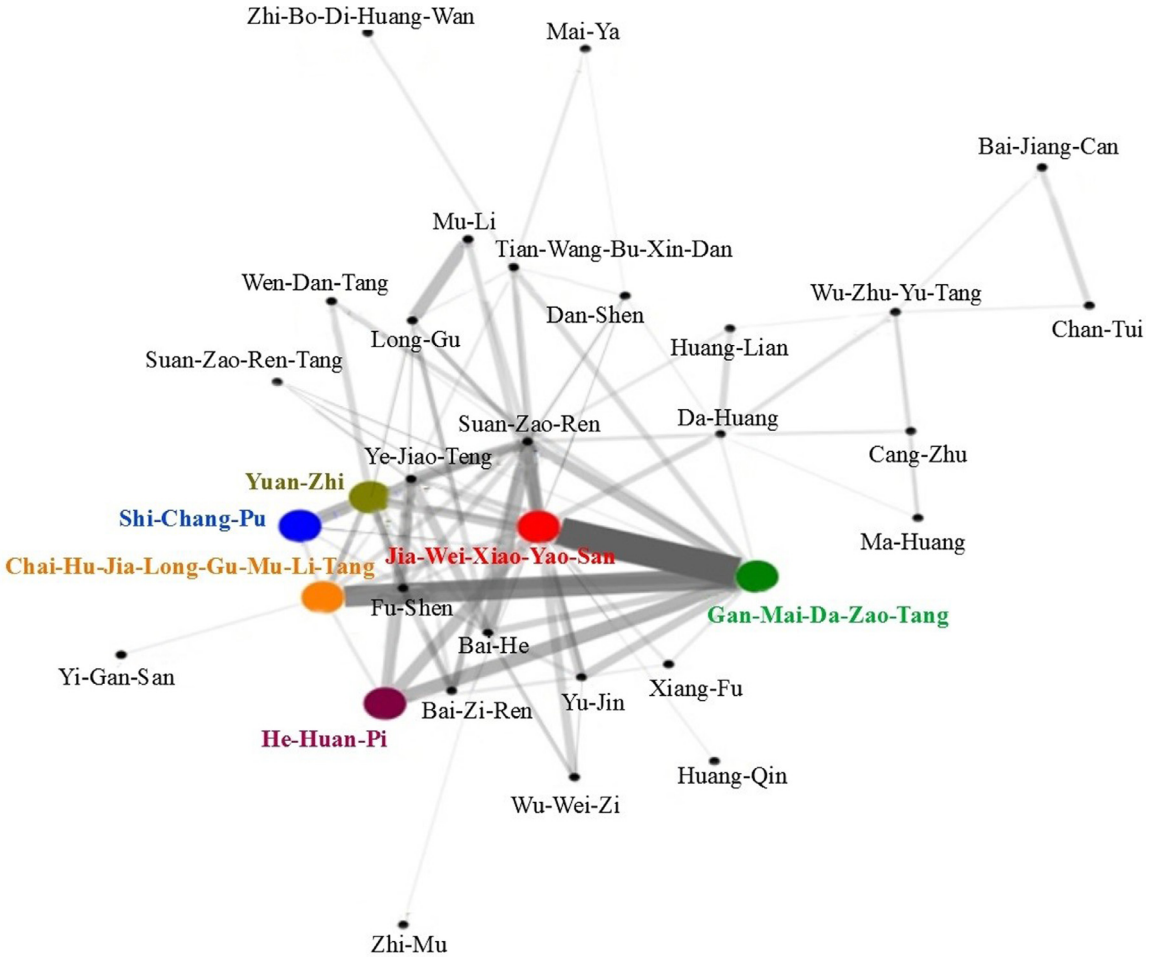

Fig. 2. The core pattern of Chinese formulae and single herbs usage for depressive disorders. The number of combinations between a certain CHM and co-prescribed CHM was used to determine the width of the line connecting them, and the thicker and darker line showed the more frequently co-prescribed between CHMs in the network.

models.[29] In human study, *Tian-Wang-Bu-Xin-Wan* showed a significant effect when combined with dormancy hygiene education when it was used to treat insomnia patients.[30] *Suan-Zao-Ren-Tang* would appear to have a sedative effect when tested in pharmacological and clinical studies.[31,32] When *Wen-Dan-Tang* is examined, several clinical and case studies have revealed that it is able to relieve the symptoms of somatic disorders[33] and melancholia.[34] The next formula, *Yi-Gan-San*, has been demonstrated to prevent an accumulation of cerebral Aβ while bringing about a reduction in anxiety-like behaviors[35]; these were preclinical studies. Other recent studies have found that this formula improves the quality of sleep when psychological insomnia is present,[36] as well as being able to ameliorate the psychiatric symptoms of both dementia and borderline personality disorder, including low mood, anxiety, and irritability.[37,38] A meta-analysis found that a combination of *Gui-Pi-Tang* and antidepressants was able to ameliorate the depressed symptoms better than antidepressants alone.[39] Finally, *Ban-Xia-Hou-Po-Tang* in a number of current studies and case reports has been shown to be effective when treating depression,[40] anxiety,[41] and insomnia.[42]

Most of the common formulae in this study are frequently used by TCM practioners to treat insomnia, depression, and anxiety, the exception being *Wu-Zhu-Yu-Tang*. By way of contrast, the latter formula is widely used to treat headache and migraine. Experimental studies and randomized controlled trials have reported that it is useful when treating headache.[43,44] This formula also has an anti-emetic effect when tested using animal models.[45] Thus, TCM physicians may be using *Wu-Zhu-Yu-Tang* to treat the physical symptoms of DD, including headache and nausea, rather than the depression itself.[46]

Table 3 presented the top ten most frequent single herbs used for DD in Taiwan. The most commonly prescribed single herb for DD from 2002 to 2011 was *Suan-Zao-Ren*. Sanjoinine A, one of *Suan-Zao-Ren* active compounds, has been shown to have an anti-anxiety effect using a mouse model; it seems to act increasing chloride influx, activating GAD65/67 expression, and thus increasing GABA transmission.[47] Another main constituent of this herb is jujuboside, and this has been reported to have a sedative-hypnotic effect.[48]

Da-Huang is used as a purgative medicine in TCM and is often used to treat constipation. Modern experimental studies have proven that rhubarb, the main component of *Da-Huang*, increases the contractile frequency of gastric body circular muscle and improves gut motility.[49,50] According to the study of Haug et al., depression is often associated with constipation.[51] Lifestyle and diet changes during depression such as a decrease in physical activity, the consumption of a lot of foods that are high in sugar or fat, and/or a loss in appetite, might be the reasons for constipation in depressive patients. In addition to the above, one of the side effects of antidepressants is constipation[6] and therefore it seems likely that TCM physicians might be using *Da-Huang* to relieve these symptoms/side-effects in depressive patients.

Yuan-Zhi has been shown to have antidepressant,[52] anti-stress,[53] anxiolytic, sleep-enhancing,[54] and anti-inflammatory ac-

tivities.[55] The underlying mechanisms would seem to include increasing the expression of CAM-L1, pCREB and BDNF in the hippocampus, protecting and bring about the proliferation of neurons, inhibiting norepinephrine in locus coeruleus, stimulating various GABAergic systems, suppressing various noradrenergic systems, and restraining the NF-κB/MAPK pathways. Moreover, several main chemicals in *Yuan-Zhi*, including polygalasaponin XXXII and onjisaponin B, have been shown to ameliorate cognitive impairments using *in vivo* studies.[56,57]

Studies about TCM for the treatment of insomnia have indicated that *Ye-Jiao-Teng* is one of the most frequently used herbs used to treat sleep disorders.[58] In TCM terms, its action is related to the nourishment of the Heart Yin and Blood, as well as calming the Spirit; thus, it could be affecting the Heart Yin Deficiency or Heart Blood Deficiency that are associated with insomnia and irritability. In addition, *Ye-Jiao-Teng* has shown to have a sedative-hypnotic effect using mouse and rat models[59] as well as showing anti-oxidant activity in an *in vitro* study.[60]

The major constituents of *Bai-He* and *He-Huan-Pi* have been reported to have antidepressant effects.[61,62] Two recent *in vivo* studies have revealed that *He-Huan-Pi* had an anti-anxiety effect via the regulation of neurotransmitters[63] and the serotonergic nervous system.[64] Additionally, a study used a Chinese formula that consisted of *He-Huan-Pi, Suan-Zao-Ren, Bai-Shao* and *Bai-Zi-Ren* using a depressed mice model indicated that this formula was able to reduce the immobility time of depressed mice by inhibiting the monoamine oxidase enzyme system, as well as by increasing serotonin and noradrenaline levels.[65]

If we examine research available on *Dan-Shen*, a pharmacological study has shown that it has a sedative-hypnotic effect when combined with *Suan-Zao-Ren*; the results suggest that a combination of these two herbs prolongs sleeping time, as well as reducing sleep latency.[66] Magnesium lithospermate B, the active compound extracted from *Dan-Shen*, has been reported to have an antidepressant-like effect using a rat model.[67] Furthermore, curcumin, which is the main component of *Yu-Jin*[68] has been shown to reduce depression and anxiety symptoms.[69] The possible mechanisms behind this antidepressant activity of curcumin seem to be a promotion of hippocampal BDNF and ERK levels.[70] In this context curcumin also has anti-inflammatory effects,[71] enhances neurotransmitters,[72] and suppresses monoamine oxidase.[73] Finally, *Fu-Shen* has a long history in TCM of being used for the treatment of insomnia and memory disorders.[74]

In TCM, one disease can include various TCM syndromes and these are used to guide the practitioner toward a treatment principle and whereby to specific herbs and herbal formulae that can be used for treatment. However, one formula or one single herb alone may not alleviate all the symptoms or signs with different severity the patients have because there are differences in the effects and targets of each formula or each single herb. In addition, as mentioned above, DD is through to involve various mechanisms.[5] Therefore, TCM physicians often combine different formulae and single herbs to enhance the treatment depending on a specific patient's symptoms and signs. In this study, we aimed to investigate in clinical practice which formulae and single herbs TCM physicians usually combine together to treat DD; thus, the hundred most common combinations found in formulae and single herbs were analyzed to examine the core prescription pattern used to treat DD. The results showed that the core pattern was the association of *Gan-Mai-Da-Zao-Tang, Jia-Wei-Xiao-Yao-San, Chai-Hu-Jia-Long-Gu-Tang, He-Huan-Pi, Yuan-Zhi* and *Shi-Chang-Pu* (Fig. 2). In the famous classic TCM book "Essentials from the Golden Cabinet" *Gan-Mai-Da-Zao-Tang* is mentioned as a treatment for "*Zang Zao*" one of the traditional terms for DD. On the other hand, *Jia-Wei-Xiao-Yao-San* has been used to treat Liver Qi stagnation by turning it towards Heat when there is underlying Spleen and Blood Deficiency, which is also related to depressive disorders. The clinical manifestations associated with *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang* include anxiety, insomnia, irritability, agitation, depression, fatigue and so on. In modern studies, these three formulae have been found to have anti-depressant as well as sedative effects via a variety of mechanisms. As discussed above, *He-Huan-Pi* and *Yuan-Zhi* seem to alleviate depression-like or anxiety-related behaviors, as well as reduce inflammatory activity, when tested using animal models. In addition, *Yuan-Zhi* gas been shown to ameliorate cognitive impairment, which ought to be helpful when treating DD. *Rhizoma Acori Tatarinowii*, used in TCM as *Shi-Chang-Pu*, has been shown to have antidepressant activity[75] both *in vivo* and *in vitro*. Moreover, *Yuan-Zhi* and *Shi-Chang-Pu* together have been demonstrated to have an anti-amnestic effect on memory impairment.[76] In summary, because DD involve many different biological mechanisms and no single formula or single herb is able to affect all the pathways involved in a given disease, a combination of a number of different TCM medicines is necessary. Moreover, several previous studies in Taiwan have shown that a combination of several formulae and single herbs could improve some diseases.[77,78] Therefore, the core pattern described in Fig. 2 provides a significant number of potential candidates that can be used in the future in new pharmacological/clinical trials targeting DD.

There are some limitations to this study. Firstly, this study did not include folk medicines or herbal diets that may have been directly purchased by patients from TCM herbal pharmacies; thus, the use of CHM among depressed patients might have been underestimated. Secondly, this study has only focused on the utilization of CHM in patients with DD; specifically, the utilization of acupuncture, and/or various other TCM treatments, which may also have been offered by TCM practitioners, at the same time as the TCM, in order to treat depression, are not included in this study and have not investigated.

In conclusion, this study describes the Chinese herbal medicine prescription patterns of patients with DD. *Gan-Mai-Da-Zao-Tang* is the most commonly prescribed formula, and *Suan-Zao-Ren* is the most commonly prescribed single herb. The core prescription pattern comprises *Gan-Mai-Da-Zao-Tang, Jia-Wei-Xiao-Yao-San, He-Huan-Pi, Yuan-Zhi, Shi-Chang-Pu*, and *Chai-Hu-Jia-Long-Gu-Mu-Li-Tang*. Although previous studies have shown that CHM can be efficacious in relieving the symptoms of DD, there have been only a limited number of such studies, and often their quality is low. Therefore, further pharmacological studies, as well as clinical trials, need to be conducted to examine the mechanisms, the efficacy and the safety of this CHM core prescription pattern in depression treatments.

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Authors contributions

DNHT: Conceptualization; Methodology; Formal Analysis; Writing - Original draft. IHH and FJC: Investigation; Data Curation. YPC, CMC, JLY and TPW: Conceptualization; Formal Analysis. SJT, CHH, and FPC: Writing – Review & Editing. YYK: Supervision; Formal Analysis; Writing – Review & Editing. All authors: approval of the final version of the manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

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Ethical statement

This study was performed under the recognition of the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB-2018-03-010CC).

Data availability

The data that support the findings of this study are available from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by National Health Research Institutes but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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