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ORIGINAL RESEARCH

Coprescription of Chinese herbal medicine and Western medication among female patients with breast cancer in Taiwan: analysis of national insurance claims

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Background: Many female breast cancer (FBC) patients take Chinese herbal medicine (CHM) and Western medication (WM) concurrently in Taiwan. Despite the possibility of interactions between the CHM and WM mentioned in previous studies, the pattern of these coprescriptions in FBC patients remains unclear. Hence, the aim of the present study is to investigate the utilization of coprescriptions of CHM and WM among the FBC patients in Taiwan.

Methods: The study was a cross-sectional survey using the sampled cohort in 2009 obtained from the National Health Insurance Research Database in Taiwan. There were 3,507 FBC patients identified from the registry for catastrophic illness patients. Ambulatory visit records, corresponding prescriptions, and the data of beneficiaries belonging to the FBC patients were further extracted. A total of 1,086 FBC patients used CHM at least once. CHM and WM prescribed within any overlapping duration were defined as coprescriptions.

Results: There were 868 (80.0%) patients simultaneously receiving CHM and WM. A total of 4,927 CHM prescriptions and 6,358 WM prescriptions were prescribed concurrently. Among these coprescriptions, the most frequently used CHM was jia-wei-xiao-yao-san (21.2%), and the most frequently coprescribed WM was acetaminophen (38.9%), followed by tamoxifen (25.5%). There were 346 patients using systemic adjuvant therapy and CHM concurrently. The most commonly coprescribed CHM with chemotherapy, endocrine therapy, and trastuzumab was xiang-sha-liu-jun-zi-tang, jia-wei-xiao-yao-san, and zhi-gan-cao-tang, respectively.

Conclusion: The combined use of CHM with WM is prevalent. The main purpose of combining CHM with systemic cancer treatment is to alleviate the treatment-related adverse effects. However, the combination may result in the potential risk of drug–herb interactions. Further clinical studies are needed to evaluate the efficacy and safety of the CHM and WM coprescriptions for FBC patients.

Keywords: drug utilization patterns, complementary and alternative medicine, pharmacoepidemiology

Introduction

Breast cancer is the most frequent cancer and the chief cause of cancer death among women in Taiwan and worldwide.[1,2] The mortality rate of breast cancer has declined, due to the popularly used screening mammography and the greater use of adjuvant therapies in recent decades.[3] Modern systemic adjuvant treatments, including cytotoxic chemotherapy, endocrine therapy, and anti-human epidermal growth factor receptor 2 (anti-HER2) therapy, should be selected based on the tumor size, grade, hormone-receptor content, and HER2 status.[4–7] However, treatment-related adverse effects, such as fatigue, nausea,

vomiting, hot flashes and other menopausal symptoms, cardiac toxicity, etc, make patients unable to tolerate treatment and lead them to seek additional help.[8]

Many breast cancer patients use complementary and alternative medicine for cancer treatment, immune system enhancement, and symptom relief.[9,10] Traditional Chinese medicine (TCM), including Chinese herbal medicine (CHM) and acupuncture, is the most popular complementary and alternative medicine modality and plays an important role in the Chinese population.[11–13] A previous study, conducted in Shanghai, the People's Republic of China, showed that 76.8% of breast cancer patients used CHM therapy after a diagnosis of breast cancer.[9] In Taiwan, Lai et al also found that 81.5% of female breast cancer (FBC) patients used TCM services and received CHM in 76.8% of visits during the 10-year study period.[14] In the survey conducted by Lin and Chiu, 35.6% of breast cancer patients used TCM during the 1-year observation period in Taiwan, and CHM (80.5%) was the most commonly used therapy.[15] All the studies revealed that the vast majority of the CHM users with breast cancer concurrently used Western medication (WM). This common practice raises concerns about the potential problems of drug–herb interactions.

TCM service is popular in the modern health system covered by the National Health Insurance (NHI) in Taiwan.[11,16] Despite the possibility of interactions between CHM and WM mentioned in previous reports, the pattern of coprescribed CHM and WM in breast cancer patients remains unclear. Hence, the aim of the present study is to investigate the utilization of coprescriptions of CHM and WM among patients with breast cancer in Taiwan.

Materials and methods

Data resources

The NHI program in Taiwan was implemented in 1995 and has covered approximately 98% of the total population of Taiwan in recent years (http://nhird.nhri.org.tw/en/index.htm). Both Western medicine and TCM services are covered by NHI. TCM is only reimbursed by NHI for ambulatory care, not for inpatient care. Both claims of Western medicine and TCM visits are required to record diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system for reimbursement.

All electronic claim data under the NHI Research Database (NHIRD) project are released by the Bureau of NHI (BNHI) for research and are further managed by the National Health Research Institutes (NHRI).[17] The identification numbers of patients and care providers are deidentified before being sent to the NHRI and are further encrypted before being released to each researcher by the NHRI. Thus, the researchers cannot identify the patients or the care providers. However, the cryptographically scrambled identification numbers remain unique for record linking within the datasets. The present study was exempted from a full review by the Institutional Review Board of the Taipei Veterans General Hospital.

We obtained the database of the complete registry for catastrophic illness patients (RCIP) since 1997 (HV1997–HV2009) and the sampled cohort file (Longitudinal Health Insurance Database 2005, LHID2005) in 2009, including the registry for beneficiaries (ID2009), ambulatory visit records (CD2009), and corresponding prescription files (OO2009). The RCIP includes all approved cases of catastrophic illness, including breast cancer. Patients with catastrophic illness should submit the pathology and related laboratory reports for registration with RCIP. The approved cases can waive the copayment for each ambulatory visit and hospitalization.

Study sample

This was a cross-sectional study. Recruited subjects were FBC patients. Initially, we identified the FBC patients who had ever been registered with a malignant neoplasm of female breast (ICD-9-CM code: 174) from the RCIP. Ambulatory visit records, corresponding prescriptions, and the data of beneficiaries belonging to the FBC patients among the sampled cohort (LHID2005) in 2009 were further extracted by linking with the cryptographic identification numbers.

The FBC patients with at least one TCM visit in 2009 were defined as TCM users. Among TCM users, those who had ever received CHM prescriptions were defined as CHM users. All diagnoses of each CHM visit were considered. We tried to find the most frequently coprescribed CHM and WM and the most commonly coprescribed CHM with systemic adjuvant therapy among FBC patients in 2009. CHM and WM prescribed within any overlapping duration were defined as coprescriptions. Figure 1 illustrates the framework of the CHM users among FBC patients and corresponding prescription selection.

Study drugs

In Taiwan, CHM generally presents as Chinese herbal products (CHP), which were concentrated herbal extract, or as a traditional form (crude drug slices processed for decoction). However, only CHPs produced by the Good

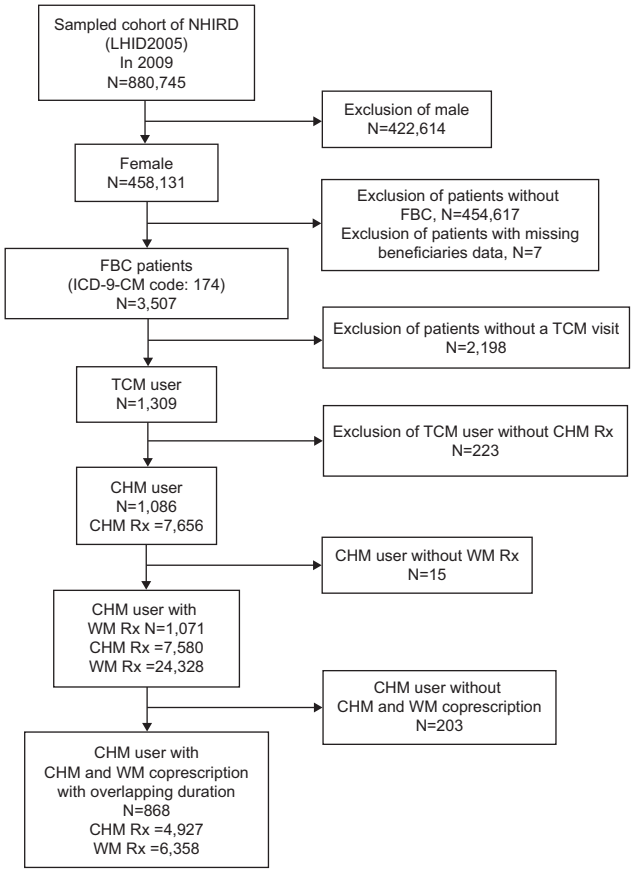

Figure 1 Framework of CHM users among FBC patients and corresponding prescriptions selection.
Abbreviations: NHIRD, National Health Insurance Research Database; LHID, Longitudinal Health Insurance Database; FBC, female breast cancer; TCM, traditional Chinese medicine; CHM, Chinese herbal medicine; Rx, prescription; WM, Western medication; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Manufacturing Practice-certified pharmaceutical companies and prescribed by licensed TCM physicians were reimbursed by the NHI. CHPs include single herbs or herbal formulas composed of two or more herbs. We downloaded all the items of the reimbursed CHPs and WM from the BNHI website.[18] Detailed information of CHPs, including constituents, was obtained from the website of the Committee on Chinese Medicine and Pharmacy.[19] In addition, WM that was composed of more than one drug was classified by the Anatomical Therapeutic Chemical (ATC) classification system.[20]

Systemic adjuvant agents for breast cancer in the study were specified, based on reimbursement. Chemotherapeutic drugs included cisplatin, carboplatin, cyclophosphamide, fluorouracil, capecitabine, gemcitabine, methotrexate, doxorubicin, epirubicin, mitoxantrone, vinorelbine, vinblastine, docetaxel, paclitaxel, and etoposide. Drugs for endocrine therapies included selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), luteinizing hormone-releasing hormone agonists, fluoxymesterone, and megestrol. SERMs included tamoxifen and toremifene. AIs included anastrozole, letrozole, and exemestane. The luteinizing hormone-releasing hormone agonists included goserelin and leuprolide. Trastuzumab was the only included HER2-directed agent.

Data analysis

Microsoft SQL Server 2008 (Microsoft Corporation, Redmond, WA, USA) was used for data management and computing. The statistical analysis of the data in this study was performed using PASW Statistics for Windows, version 18.0 (SPSS, Inc, Chicago, IL, USA). Descriptive statistics were used for the utilization of CHM and WM coprescriptions in FBC patients.

Results

Patient demographics

A total of 3,507 FBC patients had ambulatory visits in the sampled cohort (LHID2005) in 2009. Of these, 1,309 (37.3%) were TCM users, and 1,086 (31.0%) were CHM users. The detailed demographics of the CHM users with FBC are presented in Table 1. Among CHM users with FBC, the highest proportion of patients was 50–59 years of age (38.7%). The majority lived in the northern area (49.2%) and the highly urbanized towns (35.6%) of Taiwan. The most frequent insurance amount range was about 20,000–39,999 New Taiwan Dollars (41.2%). More than 60% of CHM users had been diagnosed with breast cancer <5 years. About 43.9% of CHM users were under systemic adjuvant treatment, and 32.6% of the patients received endocrine therapy alone during 2009. Young patients were more likely to use CHM only.

Diagnoses

The most common diagnosis for CHM users was "general symptoms" (24.7%); the second was "malignant neoplasm of female breast" (21.8%). Approximately one-half of CHM users looked for relieving "symptoms, signs, and ill-defined conditions" (49.6%), and the others used CHM to treat respiratory diseases (31.5%), musculoskeletal diseases (27.7%), digestive diseases (27.6%), and neoplasms (23.0%) (Table 2).

Coprescriptions of CHM and WM

Among 1,086 FBC patients who were CHM users, 1,071 were under treatment with WM. There were 868 (80.0%) patients simultaneously receiving CHM and WM. A total of 4,927 CHM prescriptions and 6,358 WM prescriptions were

Table 1 Demographics of CHM users among FBC patients in Taiwan, 2009

	Patients with CHM and WM coprescription		Patients without CHM and WM coprescription		Total	
	#	%	#	%	#	%
Patient #	868		218		1,086	
Age (years)						
<30	0	0.0	4	1.8	4	0.4
30–39	42	4.8	13	6.0	55	5.1
40–49	200	23.0	56	25.7	256	23.6
50–59	324	37.3	96	44.0	420	38.7
60–69	186	21.4	41	18.8	227	20.9
70–79	93	10.7	7	3.2	100	9.2
≥80	23	2.6	1	0.5	24	2.2
Diagnostic year for FBC						
Before 2004	334	38.5	99	45.4	433	39.9
2004–2009	534	61.5	119	54.6	653	60.1
Geographical location						
Northern	421	48.5	113	51.8	534	49.2
Central	165	19.0	45	20.6	210	19.3
Southern	259	29.8	58	26.6	317	29.2
Eastern	23	2.6	2	0.9	25	2.3
Urbanization level						
1 (highest)	308	35.5	79	36.2	387	35.6
2	252	29.0	58	26.6	310	28.5
3	98	11.3	33	15.1	131	12.1
4	106	12.2	27	12.4	133	12.2
5 (lowest)	104	12.0	21	9.6	125	11.5
Insurance amount (NTD)						
Fixed premium and dependent	251	28.9	61	28.0	312	28.7
1–19,999	156	18.0	32	14.7	188	17.3
20,000–39,999	351	40.4	96	44.0	447	41.2
≥40,000	110	12.7	29	13.3	139	12.8
Current systemic adjuvant treatment[a]						
CT[b]	47	5.4	10	4.6	57	5.2
ET[c]	330	38.0	24	11.0	354	32.6
Trastuzumab	0	0.0	0	0.0	0	0.0
CT + ET	45	5.2	6	2.8	51	4.7
CT + trastuzumab	10	1.2	0	0.0	10	0.9
ET + trastuzumab	1	0.1	0	0.0	1	0.1
CT + ET + trastuzumab	4	0.5	0	0.0	4	0.4
No systemic adjuvant treatment	431	49.7	178	81.7	609	56.1

Notes: [a]Patients have received systemic adjuvant treatment with or without coprescriptions of CHM. [b]Included cisplatin, carboplatin, cyclophosphamide, fluorouracil, capecitabine, gemcitabine, methotrexate, doxorubicin, epirubicin, mitoxantrone, vinorelbine, vinblastine, docetaxel, paclitaxel, and etoposide. [c]Included selective estrogen receptor modulator (tamoxifen, toremifene), aromatase inhibitor (anastrozole, letrozole, exemestane), luteinizing hormone-releasing hormone agonist (goserelin, leuprolide), fluoxymesterone, megestrol.

Abbreviations: CHM, Chinese herbal medicine; FBC, female breast cancer; WM, Western medication; NTD, New Taiwan Dollars; CT, chemotherapy; ET, endocrine therapy.

prescribed concurrently during the study period. Table 3 presents the most commonly used CHM and WM in coprescriptions among FBC patients in Taiwan during 2009. In these coprescriptions, the most frequently used CHM was jia-wei-xiao-yao-san (JWXYS) (21.2%), and the most frequently coprescribed WM was acetaminophen (38.9%), followed by tamoxifen (25.5%).

According to the ATC classification system, analgesics, cough and cold preparations, psycholeptics (including anxiolytics and hypnotics), drugs for acid-related disorders, and endocrine therapy were the most common WM used concurrently with CHM.

There were 346 CHM users receiving systemic adjuvant therapy concurrently. Table 4 shows the most frequently coprescribed CHM with different types of systemic adjuvant therapy. Xiang-sha-liu-jun-zi-tang (27.3%) and zhi-gan-cao-tang (40.0%) were the most commonly used CHM with chemotherapy and anti-HER2 therapy,

Table 2 Main reasons for CHM use among FBC patients in Taiwan, 2009

Main reasons		# patients (n=1,086)	%
ICD-9-CM code range[a]	Disease categories		
780–799	Symptoms, signs, ill-defined conditions	539	49.6
460–519	Diseases of respiratory system	342	31.5
710–739	Diseases of musculoskeletal system, connective tissue	301	27.7
520–579	Diseases of digestive system	300	27.6
140–239	Neoplasms	250	23.0
800–999	Injury, poisoning	140	12.9
580–629	Diseases of genitourinary system	135	12.4
320–389	Diseases of nervous system, sense organs	82	7.6
680–709	Diseases of skin, subcutaneous tissue	73	6.7
390–459	Diseases of circulatory system	65	6.0
240–279	Endocrine, nutritional, metabolic diseases, immunity disorders	40	3.7
290–319	Mental disorders	33	3.0
001–139	Infectious, parasitic diseases	14	1.3
280–289	Diseases of blood, blood-forming organs	9	0.8
740–759	Congenital anomalies	4	0.4
630–679	Complications of pregnancy, childbirth, puerperium	2	0.2

Note: [a]No patients with the following ICD-9-CM codes were diagnosed: 760–779; V01–V89; E800–E999.
Abbreviations: CHM, Chinese herbal medicine; FBC, female breast cancer; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification.

respectively. In addition, JWXYS was the most popular CHM coprescribed with SERMs or AIs. The ingredients of CHPs mentioned in the text are shown in Tables S1 and S2.

Discussion

To our knowledge, this study is the first population-based pharmacoepidemiology survey of CHM and WM coprescriptions among patients with FBC in Taiwan. Our results

Table 3 Most commonly used CHM and WM in coprescriptions among FBC patients in Taiwan, 2009

CHM			WM		
Chinese herbal products (Chinese name)	# patients (%) (n=868)	# prescriptions (%) (n=4,927)	Drugs[a]	# patients (%) (n=868)	# prescriptions (%) (n=6,358)
Jia-wei-xiao-yao-san	184 (21.2)	495 (10.0)	Acetaminophen	338 (38.9)	706 (11.1)
Yan-hu-suo	121 (13.9)	230 (4.7)	Tamoxifen	221 (25.5)	908 (14.3)
Bei-mu	119 (13.7)	284 (5.8)	Antacids	217 (25.0)	431 (6.8)
Huang-qin	116 (13.4)	299 (6.1)	Cough suppressants and expectorants, combinations	199 (22.9)	404 (6.4)
Dan-shen	109 (12.6)	319 (6.5)	Diclofenac	159 (18.3)	255 (4.0)
Jie-geng	108 (12.4)	231 (4.7)	Ambroxol	115 (13.2)	181 (2.8)
Suan-zao-ren	102 (11.8)	256 (5.2)	Intravenous fluids[b]	104 (12.0)	325 (5.1)
Shao-yao-gan-cao-tang	100 (11.5)	210 (4.3)	Zolpidem	104 (12.0)	273 (4.3)
Ban-xia-xieh-xin-tang	98 (11.3)	260 (5.3)	Nasal decongestants for systemic use	104 (12.0)	196 (3.1)
Shu-jing-huo-xie-tang	94 (10.8)	189 (3.8)	Dimethicone	85 (9.8)	142 (2.2)
Shou-wu-teng	93 (10.7)	251 (5.1)	Alprazolam	84 (9.7)	229 (3.6)
Huang-qi	92 (10.6)	270 (5.5)	Lorazepam	82 (9.4)	211 (3.3)
Suan-zao-ren-tang	91 (10.5)	238 (4.8)	Domperidone	81 (9.3)	148 (2.3)
Ge-gen-tang	91 (10.5)	172 (3.5)	Amlodipine	74 (8.5)	216 (3.4)
Mai-dong	90 (10.4)	197 (4.0)	Cimetidine	73 (8.4)	134 (2.1)
Ping-wei-san	89 (10.3)	227 (4.6)	Mefenamic acid	71 (8.2)	120 (1.9)
Chuan-xiong-cha-tiao-san	88 (10.1)	218 (4.4)	Corticosteroids, combinations with antibiotics, topical use	71 (8.2)	110 (1.7)
Yin-qiao-san	88 (10.1)	160 (3.2)	Ibuprofen	69 (7.9)	110 (1.7)
Ge-gen	84 (9.7)	217 (4.4)	Chlorzoxazone	69 (7.9)	106 (1.7)
Xuan-shen	84 (9.7)	208 (4.2)	Dextromethorphan	69 (7.9)	99 (1.6)

Note: [a]Western medication composed of more than one drug was classified by the ATC classification system; [b]such as dextrose solutions, normal saline solutions.
Abbreviations: CHM, Chinese herbal medicine; WM, Western medication; FBC, female breast cancer; ATC, Anatomical Therapeutic Chemical classification system.

Table 4 Most commonly used CHM coprescribed with systemic adjuvant treatment among FBC patients in Taiwan, 2009

Chinese herbal products (Chinese name)	# patients (%) (n=346)	# prescriptions (%) (n=2,125)
With chemotherapy	**66**	**357**
Xiang-sha-liu-jun-zi-tang	18 (27.3)	61 (17.1)
Jia-wei-xiao-yao-san[a,b]	12 (18.2)	24 (6.7)
Huang-qi	11 (16.7)	32 (9.0)
Dan-shen	11 (16.7)	27 (7.6)
Pu-gong-ying	11 (16.7)	26 (7.3)
Ban-xia-xieh-xin-tang	11 (16.7)	19 (5.3)
Sheng-mai-san	10 (15.2)	29 (8.1)
Mu-dan-pi	10 (15.2)	18 (5.0)
Gan-lu-yin[c]	9 (13.6)	49 (13.7)
Bai-hua-she-she-cao	9 (13.6)	41 (11.5)
Sha-ren	9 (13.6)	22 (6.2)
Fu-ling	9 (13.6)	21 (5.9)
Bai-zhu	9 (13.6)	18 (5.0)
Suan-zao-ren	9 (13.6)	14 (3.9)
Huang-qin	9 (13.6)	14 (3.9)
With endocrine therapy	**301**	**1,801**
SERM	**221**	**1,320**
Jia-wei-xiao-yao-san[a,b]	51 (23.1)	177 (13.4)
Suan-zao-ren-tang[d]	32 (14.5)	103 (7.8)
Ban-xia-xieh-xin-tang	31 (14.0)	55 (4.2)
Suan-zao-ren	29 (13.1)	88 (6.7)
Bei-mu	29 (13.1)	74 (5.6)
Tian-wang-bu-xin-dan[a,c]	29 (13.1)	73 (5.5)
Yan-hu-suo	28 (12.7)	58 (4.4)
Shou-wu-teng	27 (12.2)	97 (7.3)
Yu-jin	26 (11.8)	97 (7.3)
Huang-qi	25 (11.3)	89 (6.7)
Dan-shen	25 (11.3)	77 (5.8)
Jie-geng	25 (11.3)	52 (3.9)
AI	**85**	**462**
Jia-wei-xiao-yao-san[a,b]	15 (17.6)	32 (6.9)
Huang-qin	13 (15.3)	22 (4.8)
Shao-yao-gan-cao-tang[b]	12 (14.1)	23 (5.0)
Jie-geng	12 (14.1)	21 (4.5)
Gan-cao	11 (12.9)	30 (6.5)
Bai-shao[b]	11 (12.9)	22 (4.8)
Ban-xia-xieh-xin-tang	10 (11.8)	56 (12.1)
San-qi	10 (11.8)	23 (5.0)
Bei-mu	10 (11.8)	23 (5.0)
Zhi-qiao	10 (11.8)	18 (3.9)
Du-huo-ji-sheng-tang[b–d]	10 (11.8)	17 (3.7)
Huang-lian	10 (11.8)	16 (3.5)
Xu-duan	10 (11.8)	11 (2.4)
Other endocrine therapies	**4**	**27**
With anti-HER2 therapy (trastuzumab)	**10**	**95**
Zhi-gan-cao-tang	4 (40.0)	13 (13.7)
Gan-lu-yin[c]	3 (30.0)	21 (22.1)
Sha-ren	3 (30.0)	9 (9.5)
Xiang-sha-liu-jun-zi-tang	3 (30.0)	8 (8.4)
Pu-gong-ying	3 (30.0)	5 (5.3)
Zhen-ren-huo-ming-yin[a]	3 (30.0)	5 (5.3)
Tian-hua-fen	3 (30.0)	5 (5.3)

Notes: [a]Chinese herbal products containing *Angelicae sinensis radix*. [b]Chinese herbal products containing *Paeoniae radix alba*. [c]Chinese herbal products containing *Rehmanniae radix praparata*. [d]Chinese herbal products containing *Chuanxiong rhizoma*.

Abbreviations: CHM, Chinese herbal medicine; FBC, female breast cancer; SERM, selective estrogen receptor modulator; AI, aromatase inhibitor; HER2, human epidermal growth factor receptor 2.

highlight the importance of further studies required to evaluate the clinical impact of these coprescriptions for FBC patients.

CHM utilization

From the present study, the high prevalence (37.3%) of TCM usage among FBC patients in Taiwan is in accordance with the survey conducted by Lin and Chiu.[15] Breast cancer patients are more likely to use TCM than patients with other cancers.[21,22] CHM is the dominant type of TCM used by FBC patients and the general population.[11,16] In our study, 83.0% (1,086/1,309) TCM users received CHM treatment. We also found that 1,071 (98.6%) CHM users of FBC patients received both CHM and WM during 2009.

Among them, 868 CHM users took CHM and WM concurrently. In the present study, the most common diagnoses for CHM users of FBC patients were "malignant neoplasm of female breast" and "general symptoms", such as nausea, vomiting, fatigue, etc. However, treatment for breast cancer accounted for only 21.8%, which is in accordance with the findings of the previous survey in Taiwan.[14,15] This is significantly lower than the results from Shanghai, which found that more than 90% of FBC patients used CHM for fighting cancer.[9] The different results may also relate to the different methods of data collection used by our study and the study from Shanghai.

Because the study from Shanghai used direct-participant interviews, it may not directly compare to our results. In addition, our study found that diseases of the digestive, respiratory, musculoskeletal, and genitourinary systems were the most common reasons for using CHM. The purposes of CHM usage are consistent with the results of the general population surveys in Taiwan.[11,16] Obviously, CHM usage among FBC patients in Taiwan may be regarded as an add-on therapy rather than a substitute modality.

Possible reasons for coprescriptions

Menopausal syndrome is the major complication among breast cancer patients under chemotherapy and endocrine therapy.[8] Menopausal complications – including hot flashes, night sweats, insomnia, etc – seriously impact the quality of life of breast cancer patients. Therefore, most of them search for management strategies. According to the study conducted in Shanghai, about 29.4% of breast cancer patients use CHM to lessen menopausal symptoms. Patients with menopausal symptoms or who had used tamoxifen in the past were prone to use CHM.[9] In coprescriptions, we found that JWXYS was the most frequently used CHM, and tamoxifen was the most commonly prescribed WM associated with FBC treatment. Furthermore, our study revealed a high coprescription rate between JWXYS and chemotherapy or JWXYS and endocrine therapy. JWXYS, also named dan-zhi-xiao-yao-san, is the principal CHM for the relief of menopausal syndrome.[23–26] The clinical effects of JWXYS were documented in the classics of traditional medicine and reported by clinical studies.[27,28] This implies that many FBC patients under modern systemic cancer treatment suffered from menopausal symptoms and sought CHM therapy concurrently. The results of the present study are compatible with the Shanghai survey.[9] Our results also found that a considerable proportion of CHM was likely to be used for insomnia when combined with SERMs. These CHM include suan-zao-ren-tang, tian-wang-bu-xin-dan, suan-zao-ren (*Ziziphi spinosae semen*) and shou-wu-teng (*Polygoni multiflori caulis*), etc.[29–34]

Musculoskeletal problems, such as arthralgia and osteoporosis, that result from AI treatment are significantly more than those caused by tamoxifen treatment.[35] Joint pain and musculoskeletal pain are the most commonly reported troublesome adverse effects from AI users.[36,37] Our results found that most CHM coprescribed with AIs was used for arthritis and pain relief. For example, du-huo-ji-sheng-tang and xu-duan (*Dipsaci radix*) are used to treat osteoarthritis, osteoporosis, and other bone diseases.[38–41] Shao-yao-gan-cao-tang is used to relieve dysmenorrhea and muscle pain.[42]

Cardiac toxicity is one of the major concerns for patients with anthracycline-based chemotherapy and trastuzumab treatment.[43,44] In contrast to anthracycline-related cardiomyopathy and heart failure, cardiotoxicity of trastuzumab is often manifested by asymptomatic left ventricular ejection fraction reduction, palpitations, and – less often – by heart failure. Sheng-mai-san is a famous herbal formula used for the treatment of heart failure and ischemic heart disease.[45] The present study found that many FBC patients treated with chemotherapy used sheng-mai-san concurrently. On the other hand, the study revealed that zhi-gan-cao-tang was one of the commonly coprescribed CHM with trastuzumab. Zhi-gan-cao-tang is traditionally used for reversing irregular cardiac rhythm.[46]

In the present study, we also found that many CHM coprescribed with chemotherapy were used for relieving gastrointestinal symptoms. The most frequently coprescribed xiang-sha-liu-jun-zi-tang is a famous formula for the treatment of functional dyspepsia.[47] Ban-xia-xie-xin-tang can mitigate nausea and vomiting caused by systemic cancer

therapy.[48,49] The other single herbs such as sha-ren (*Amomi fructus*) and bai-zhu (*Atractylodis macrocephalae rhizoma*) can modulate gastrointestinal symptoms.[50,51]

Besides relieving treatment-related symptoms, other commonly coprescribed CHM are also applied to fight cancer. For example, pu-gong-ying (*Taraxaci herba*), bai-hua-she-she-cao (*Hedyotis diffusae herba*), yu-jin (*Curcumae radix*), and zhen-ren-huo-ming-yin all have shown antitumor effects.[52–54] Huang-qin (*Scutellariae radix*) can enhance the antitumor effect.[55] Huang-qi (*Astragali radix*) has an anti-cancer effect and boosts the immune function.[56] Overall, one of the main purposes of CHM when combined with systemic cancer treatment was to alleviate the treatment-related adverse effects.

Possible interactions between CHM and SERM/anti-HER2 therapy

Recently, there was a small cohort study, and a case report found that si-wu-tang (SWT), one of the popular Chinese herbal formulas for the regulation of menstruation, might have mitogenic potential side effects on breast duct cells in long-term use.[57]

Moreover, SWT and its constituents, *Angelicae sinensis radix, Paeoniae radix alba, Chuanxiong rhizome,* and *Rehmanniae radix preparata,* have been proven to stimulate mammary duct cell growth by the activation of estrogen receptor α and HER-2 signaling in cell line studies.[58,59] Another study demonstrated that, based on in vivo and in vitro studies, SWT respectively reversed tamoxifen- and trastuzumab-induced antiproliferative effects.[60] Therefore, it is necessary to cautiously evaluate the coprescriptions of CHM and WM for breast cancer patients.

Our study found that some CHM coprescribed with SERM or with trastuzumab contained parts of the constituents of SWT. Examples are: JWXYS contains *Angelicae sinensis radix* and *Paeoniae radix alba*; suan-zao-ren-tang contains *Chuanxiong rhizoma*; and tian-wang-bu-xin-dan contains *Angelicae sinensis radix* and *Rehmanniae radix praparata*. It is still unknown whether these formulas containing these single herbs have the same potential risk to reverse tamoxifen- or trastuzumab-induced antiproliferative effects.

Furthermore, the observed results from in vitro or in vivo studies cannot be extrapolated to those in humans. It is better to remind patients to pay more attention when using CHM and tamoxifen or trastuzumab treatment concurrently. Further clinical studies are required to explore the risk of these interactions.

Limitation

Our study has several potential limitations.

First, breast cancer in situ, including ductal carcinoma in situ and lobular carcinoma in situ, was not included as a catastrophic illness in the Taiwan NHI program. In addition, some CHM services were self-paid and not covered by the NHI program, including CHM services provided by non-NHI-contracted health care institutions, or self-paid traditional-form Chinese herbal remedies, etc. The lack of above data leads to the underestimation of CHM utilization for FBC patients.

Second, due to the lack of information, including cancer stages, lab data, clinical symptoms, and survival data in NHIRD, the study was neither to evaluate the relationship between disease severities and CHM usage nor to elucidate the effects of CHM therapies.

Third, we defined coprescriptions as CHM and WM prescribed within any overlapping duration. However, we cannot verify the concurrent use of CHM and WM.

Finally, the clinical effects of interactions between CHM and SERM or CHM and anti-HER2 therapy cannot be confirmed.

Conclusion

CHM use in FBC patients is popular in Taiwan. The main purpose of CHM combined with systemic cancer treatment is to alleviate the treatment-related adverse effects. A high prescription rate of CHM combined with WM may lead to possible drug–herb interactions. Further research is needed to evaluate the clinical impact of CHM and WM coprescriptions for FBC patients.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Chinese herbal products

CHPs of single herb (Chinese name)	Ingredient herb (Latin name)
Bai-hua-she-she-cao	*Hedyotidis diffusae herba*
Bai-shao	*Paeoniae radix alba*
Bai-zhu	*Atractylodis macrocephalae rhizoma*
Bei-mu	*Fritillaria bulbus*
Dan-shen	*Salviae miltiorrhizae radix et rhizoma*
Fu-ling	*Poria*
Gan-cao	*Glycyrrhizae radix et rhizoma*
Ge-gen	*Puerariae lobatae radix*
Huang-lian	*Coptidis rhizoma*
Huang-qi	*Astragali radix*
Huang-qin	*Scutellariae radix*
Jie-geng	*Platycodonis radix*
Mai-dong	*Ophiopogonis radix*
Mu-dan-pi	*Moutan cortex*
Pu-gong-ying	*Taraxaci herba*
San-qi	*Notoginseng radix et rhizoma*
Sha-ren	*Amomi fructus*
Shou-wu-teng	*Polygoni multiflori caulis*
Suan-zao-ren	*Ziziphi spinosae semen*
Tian-hua-fen	*Trichosanthis radix*
Xuan-shen	*Scrophulariae radix*
Xu-duan	*Dipsaci radix*
Yan-hu-suo	*Corydalis rhizoma*
Yu-jin	*Curcumae radix*
Zhi-qiao	*Aurantii fructus*

Abbreviation: CHPs, Chinese herbal products.

Table S2 Chinese herbal products of herbal formulas

CHPs of herbal formula (Chinese name)	Ingredient herbs (Latin name)
Ban-xia-xieh-xin-tang	*Pinelliae rhizoma, Scutellariae radix, Zingiberis rhizoma, Ginseng radix et rhizoma, Coptidis rhizoma, Jujubae fructus, Glycyrrhizae radix et rhizoma praparata cum melle*
Chuan-xiong-cha-tiao-san	*Angelicae dahuricae radix, Glycyrrhizae radix et rhizoma, Notopterygii rhizoma et radix, Schizonepetae herba, Chuanxiong rhizoma, Asari radix et rhizoma, Saposhnikoviae radix, Menthae haplocalycis herba*
Du-huo-ji-sheng-tang	*Angelicae pubescentis radix, Taxilli herba, Eucommiae cortex, Achyranthis bidentatae radix, Asari radix et rhizoma, Gentianae macrophyllae radix, Poria, Cinnamomi cortex, Saposhnikoviae radix, Chuanxiong rhizoma, Ginseng radix et rhizoma, Glycyrrhizae radix et rhizoma, Angelicae sinensis radix, Paeoniae radix alba, Rehmanniae radix*
Gan-lu-yin	*Rehmanniae radix praparata, Ophiopogonis radix, Aurantii fructus, Glycyrrhizae radix et rhizoma praparata cum melle, Artemisiae scopariae herba, Eriobotryae folium, Dendrobii caulis, Scutellariae radix, Rehmanniae radix, Asparagi radix*
Ge-gen-tang	*Puerariae lobatae radix, Ephedrae herba, Cinnamomi ramulus, Paeoniae radix alba, Glycyrrhizae radix et rhizoma praparata cum melle, Zingiberis rhizoma recens, Jujubae fructus*
Jia-wei-xiao-yao-san	*Angelicae sinensis radix, Atractylodis macrocephalae rhizoma, Paeoniae radix alba, Bupleuri radix, Poria, Glycyrrhizae radix et rhizoma praparata cum melle, Moutan cortex, Gardeniae fructus, Zingiberis rhizoma praeparatum, Menthae haplocalycis herba*
Ping-wei-san	*Citri reticulatae pericarpium, Magnoliae officinalis cortex, Glycyrrhizae radix et rhizoma praparata cum melle, Atractylodis rhizoma, Zingiberis rhizoma recens, Jujubae fructus*
Shao-yao-gan-cao-tang	*Paeoniae radix alba, Glycyrrhizae radix et rhizoma praparata cum melle*
Sheng-mai-san	*Ginseng radix et rhizoma, Ophiopogonis radix, Schisandrae chinensis fructus*
Suan-zao-ren-tang	*Ziziphi spinosae semen, Anemarrhenae rhizoma, Poria, Chuanxiong rhizoma, Glycyrrhizae radix et rhizoma*

(*Continued*)

Table S2 (*Continued*)

CHPs of herbal formula (Chinese name)	Ingredient herbs (Latin name)
Tian-wang-bu-xin-dan	*Rehmanniae radix, Scrophulariae radix, Salviae miltiorrhizae radix et rhizoma, Angelicae sinensis radix, Schisandrae chinensis fructus, Ophiopogonis radix, Polygalae radix, Coptidis rhizoma, Platycodonis radix, Asparagi radix, Ziziphi spinosae semen, Ginseng radix et rhizoma, Poria, Platycladi semen, Rehmanniae radix praparata, Acori tatarinowii rhizoma*
Xiang-sha-liu-jun-zi-tang	*Ginseng radix et rhizoma, Atractylodis macrocephalae rhizoma, Poria, Glycyrrhizae radix et rhizoma, Citri reticulatae pericarpium, Pinelliae rhizoma, Amomi fructus, Aucklandiae radix, Zingiberis rhizoma recens*
Yin-qiao-san	*Forsythiae fructus, Lonicerae japonicae flos, Platycodonis radix, Menthae haplocalycis herba, Lophatheri herba, Glycyrrhizae radix et rhizoma, Schizonepetae herba, Sojae semen praeparatum, Arctii fructus, Phragmitis rhizoma*
Zhen-ren-huo-ming-yin	*Lonicerae japonicae flos, Citri reticulatae pericarpium, Saposhnikoviae radix, Fritillariae bulbus, Olibanum, Angelicae sinensis radix, Angelicae dahuricae radix, Trichosanthis radix, Myrrha, Gleditsiae spina, Glycyrrhizae radix et rhizoma*
Zhi-gan-cao-tang	*Glycyrrhizae radix et rhizoma praparata cum melle, Zingiberis rhizoma recens, Cinnamomi ramulus, Ginseng radix et rhizoma, Rehmanniae radix, Asini corii colla, Ophiopogonis radix, Cannabis semen, Jujubae fructus*

Abbreviation: CHPs, Chinese herbal products.