Complementary Therapies in Medicine 47 (2019) 102213

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Chinese herbal medicine therapy and the risk of overall mortality for patients with liver cancer who underwent surgical resection in Taiwan

Fuu-Jen Tsai[a,b,c,1], Xiang Liu[d,1], Chao-Jung Chen[b,e,1], Te-Mao Li[a], Jian-Shiun Chiou[f], Po-Heng Chuang[g], Cheng-Hang Ko[h], Ting-Hsu Lin[b], Chiu-Chu Liao[b], Shao-Mei Huang[b], Wen-Miin Liang[f,*], Ying-Ju Lin[a,b,**]

[a] School of Chinese Medicine, China Medical University, Taichung, Taiwan
[b] Genetic Center, Proteomics Core Laboratory, Department of Medical Research, China Medical University Hospital, Taichung, Taiwan
[c] Department of Biotechnology and Bioinformatics, Asia University, Taichung, Taiwan
[d] National Cancer Institute, National Institutes of Health, Gaithersburg, MD, USA
[e] Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan
[f] Graduate Institute of Biostatistics, School of Public Health, China Medical University, Taichung, Taiwan
[g] Division of Hepato-Gastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan
[h] Department of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan

ARTICLE INFO

Keywords:
Liver cancer
Surgical resection
Overall mortality
Chinese herbal medicine
Network analysis

ABSTRACT

Liver cancer is the sixth most diagnosed cancer globally, and the second leading cause of cancer-related deaths. Surgical resection is a procedure performed to remove cancerous tissue from the liver. Chinese herbal medicine (CHM) is a complementary natural medicine system widely used for treatment of hepatic diseases in Asian countries. We investigated the effects on overall mortality of long-term use of CHM for treatment of patients with liver cancer who underwent surgical resection at the Taiwan Center for Medicine. We identified 1504 patients with liver cancer who underwent surgical resection. Of these patients, 210 CHM users and 210 non-users were selected, and were matched for age, gender, radiotherapy, and chemotherapy prior to CHM treatment. Chi-squared test, Cox proportional hazard modeling, the Kaplan-Meier method, log-rank test, association rule mining, and network analysis were used as statistical methods in this study. CHM users showed a significantly lower risk of overall mortality than non-users (HR: 0.57, 95% CI = 0.40-0.81; $p = 0.0025$; multivariate Cox proportional hazard model), and a lower 10-year cumulative incidence of overall mortality ($p < 0.05$; log rank test). Association rule mining and network analysis suggested that Bai-Hua-She-She-Cao, Ban-Zhi-Lian, and Suan-Zao-Ren were the most effective CHMs. Therefore, we concluded that use of CHM as adjunctive therapy may reduce overall mortality in patients with liver cancer who underwent surgical resection. A list of herbal medicines with potential as future therapeutic interventions to prolong the life-span of patients with liver cancer who underwent surgical resection is also provided.

1. Introduction

Liver cancer, also called primary hepatocellular carcinoma (HCC), is the sixth most frequently diagnosed cancer globally, and is the second most common cause of cancer-related deaths.[1,2] The mortality rate of patients with liver cancer is high, with almost 800,000 deaths reported annually worldwide.[3] In Taiwan, liver cancer is the second-leading cause of death. Nearly 85% of these deaths are due to chronic viral hepatitis and cirrhosis.[4]

Surgical resection is a procedure performed to remove cancerous tissue from the liver, and is the most widely used and effective treatment for liver cancer.[5,6] Surgical resection includes local excision or

Abbreviations: CHM, Chinese herbal medicine; HR, hazard ratio; CI, confidence interval; HCC, hepatocellular carcinoma; NHIRD, National Health Insurance Research database; NHI, National Health Insurance; TCM, traditional Chinese medicine; NHRI, National Health Research Institutes; ICD-9-CM, The International Classification of Diseases 9th Revision, Clinical Modification; BZL, Ban-Zhi-Lian; BHSSC, Bai-Hua-She-She-Cao; SZR, Suan-Zao-Ren

* Corresponding author.
** Corresponding author at: School of Chinese Medicine, China Medical University, Taichung, Taiwan.
E-mail addresses: wmliang@mail.cmu.edu.tw (W.-M. Liang), yjlin.kath@gmail.com (Y.-J. Lin).
[1] Fuu-Jen Tsai, Xiang Liu, and Chao-Jung Chen contributed equally to this work.

https://doi.org/10.1016/j.ctim.2019.102213
Received 27 March 2019; Received in revised form 2 September 2019; Accepted 8 October 2019
Available online 16 October 2019

destruction of liver tissue or lesions, marsupialization of lesions of the liver, partial hepatectomy, other destruction of lesions of the liver, lobectomy of the liver, and total hepatectomy. However, the recurrence rate following surgery may be greater than 70% due to metastasis of the initial tumor or formation of new tumors. Other conventional treatments include radiotherapy, chemotherapy, interferon therapy, and anti-viral therapy.[7] Some patients may be given adjuvant therapies such as chemotherapy and/or radiotherapy following surgical resection to prevent the recurrence of liver cancer.[7,8] Chinese herbal medicine (CHM) is an adjuvant treatment that has been widely used for treatment of liver diseases in Taiwan, including HBV-induced hepatitis, HCV-induced hepatitis, liver fibrosis, and liver cancer.[9–14] CHM exerts beneficial effects on liver cancer by reducing the rate of recurrence and metastasis after surgery, alleviating symptoms of regular treatment, and protecting liver function.[15–17]

Although CHM is widely for clinical treatment of patients with liver cancer, its clinical efficacy, specifically with regard to survival rates, requires further investigation. The association between CHM prescription patterns and better survival rates in patients with liver cancer has not been characterized. Moreover, the effect of long-term use of CHM by patients with liver cancer requires further study. Therefore, we used a population-based database to investigate the demographic characteristics, cumulative incidences of overall mortality, and CHM prescription patterns for patients with liver cancer who underwent surgical resection in Taiwan.

2. Materials and methods

2.1. Data sources

The National Health Insurance Research database (NHIRD; http://nhird.nhri.org.tw/) of the National Health Insurance (NHI) program was used in this study (https://www.nhi.gov.tw/english/). The NHI program was introduced in 1995 and provides comprehensive medical care, including CHM. This program covers nearly 100% of the population in Taiwan, which is approximately 24 million individuals. The NHI program was designed as a longitudinal and retrospective cohort study in Taiwan. The data used in this study were derived from a subset of the NHIRD, which contains data on one million randomly sampled beneficiaries enrolled in the NHI program from 1996 to 2012, and is maintained and managed by The National Health Research Institute (NHRI). The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) was used for identification of the study population. Each individual was anonymized. Therefore, informed consent was not required.

2.2. Study population and variables

A total of 1504 patients with liver cancer (ICD-9-CM: 155) who underwent surgical resection (OP code: 502, 5021, 5022, 5029, 503, and 504) from 2000 to 2009 were selected from the NHI program in Taiwan for this study (Fig. 1). The surgical resection procedures included local excision or destruction of liver tissue or lesion (OP code: 502), marsupialization of lesion of liver (OP code: 5021), partial hepatectomy (OP code: 5022), other destruction of lesion of liver (OP code: 5029), lobectomy of liver (OP code: 503), and total hepatectomy (OP code: 504). Two hundred forty-two patients with more than 14 cumulative CHM treatment days within the first year of liver cancer with surgical resection were defined as CHM users. Three hundred eighteen study subjects were defined as non-CHM users who were patients with liver cancer who underwent surgical resection, but did not receive CHM. Furthermore, to reduce potential bias, CHM and non-CHM users were matched in a 1:1 ratio by age, gender, radiotherapy, and chemotherapy (Fig. S1, Fig. S**2,** Table S4, and Table S**5**). Accordingly, 210 CHM users and 210 non-CHM users were selected (Fig. 1 and Table 1). The index date was defined as the date on which the CHM treatment schedule was completed. The CHM users continued using CHMs during the study period (from the index date to the study endpoint) (Table S**8**). We used the ICD-9-CM codes from the traditional Chinese medicine (TCM) consultations (the TCM claims data) to stratify clinical visits by major categories/diagnoses (Table S9, Table S**10, and** Fig. S**4**).

Both the CHM and non-CHM user groups were followed from the index date to the date of death, the date of withdrawal from the NHI program, or the end date of the database (December 31, 2012).

2.3. Comorbidities and treatment history

Comorbidities and medications were recorded prior to the index date. Comorbidities included hypertension (ICD-9-CM: 401–405), diabetes (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), and cardiovascular diseases (ICD-9-CM: 390–459). Medications included chemotherapy (ATC code: L01; antineoplastic agents), radiotherapy (ICD-9-CM: 155 and OP code: 36001B, 36001BA, 36015B, 36002B, 36004B, 36005B, 36006B, 36009B, 36010B, 36011B, 36012B, 36013B, 36014B, 37024A1, 36018B, 36019B, 36012BCE, 36020B, and 36021C),

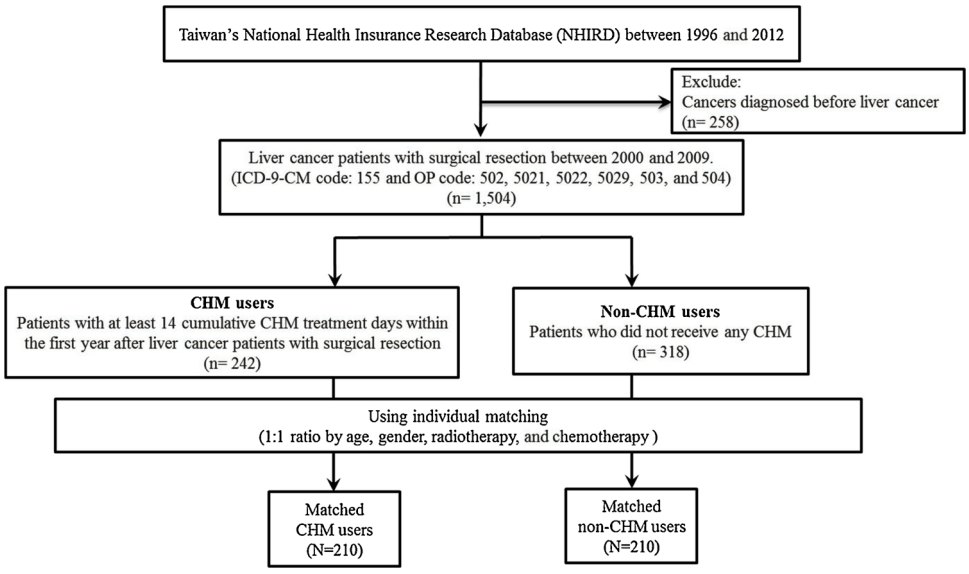


Fig. 1. Flowchart of enrollment of the study subjects.

interferon therapy (ATC code: L03AB; interferons), and anti-viral therapy (ATC code: J05AB; nucleosides and nucleotides excluding reverse transcriptase inhibitors).

2.4. Association rule and network analysis of CHM

Statistical methods for data mining (association rule and network analysis) have been used to evaluate Chinese herbal medicine prescriptions.[18–23] Since we obtained the CHM prescription list from patients with liver cancer who underwent surgical resection, we further investigated combinations of CHM herbs that were repeatedly used. In this study, we applied association rule mining to uncover the relationships of these CHM prescriptions with CHM herbs in our datasets.[20,22,23] Association rule mining is generally used in business to investigate customer purchase data. The terms "item" and "transaction" are used. In this study, the Chinese herbs were used as the "items" and the CHM prescriptions were used as the "transactions," with co-occurrences recorded (Table S1, Table S**2, and** Table 3). In association rule mining, a collection of zero or more items is called an itemset. An association rule is expressed as X →Y, where X and Y are disjoint itemsets. This expression shows the relationship between the occurrences of itemset X and itemset Y. The strength of the association using this technique was expressed as support, confidence, and lift. Support shows how often a rule is applicable to a given dataset. The support value (%) was defined as: [the frequency of prescriptions of CHM_X and CHM_Y products / total prescriptions] x 100%. Support is a measure of whether an association between X and Y happened by chance. Confidence is an indicator of how often Y appeared in transactions that contained X. The confidence value (CHM_X → CHM_Y; %) was defined as: [frequency of prescriptions of CHM_X and CHM_Y products / frequency of prescriptions of CHM_X product] x 100%. Confidence shows the reliability of the association. Lift is the ratio of observed support to expected support when X and Y are independent. The lift value was confidence value (CHM_X → CHM_Y) (%) / P (Y) (%). P (Y) (%) is as follows: [frequency of prescriptions of Y product / total prescriptions] x 100%. A lift value greater than 1 indicates that the occurrences between the two itemsets are dependent and suggests a strong co-occurrence relationship between itemsets X and Y. In this study, the association rule mining method was used for the top fifty, two-CHM combinations using the "arules_1.6" package of R software (version 3.4.3).

A network analysis method was also used to show the overall, grouped, and core CHM prescription patterns that connected CHM prescriptions, and was not restricted to two-CHM combinations.[20,22,24] In this study, network analysis was used to analyze the overall pattern of how these Chinese herbs were used together for treatment of patients with liver cancer who underwent surgical resection (Fig. 3). The network between Chinese herbs was configured using Cytoscape (https://cytoscape.org/, version 3.7.0). The red circles represent herbal formulas and the green circles represent single herbs. The sizes of the circles represent the frequency of prescription of each CHM. The lines connecting CHMs represent support values, with thicker lines representing higher support values. Darker lines represent higher lift values. The connections between CHMs are more important when the connecting lines are thicker and darker.

2.5. Ethics statement

Patient identity was kept anonymous in the NHIRD database. As such, patient consent was not required to access data from the NHIRD. Data acquisition was permitted by the Research Ethics Committee of the

Table 1
Demographic characteristics of liver cancer patients with surgical resection between CHM and non-CHM users in Taiwan (total number of subjects and matched controls).

Characteristics	Total subjects		*p*-value	Matched subjects		***p*-value**
	CHM users (N = 242) N (%)	Non-CHM users (N = 318) N (%)		CHM users (N = 210) N (%)	Non-CHM users (N = 210) N (%)	
Age (Mean ± SD)	59.14 ± 12.49	60.52 ± 13.5	0.215	58.82 ± 11.95	59.37 ± 11.42	0.63
Gender			0.069			1
Male	175 (72.31%)	251 (78.93%)		159 (75.71%)	159 (75.71%)	
Female	67 (27.69%)	67 (21.07%)		51 (24.29%)	51 (24.29%)	
Duration from liver cancer with surgical resection to the index date (day)	ND	ND	ND	159.08 ± 95.14	159.08 ± 95.14	1
Comorbidities						
Hypertension	113 (46.69%)	151 (47.48%)	0.853	99 (47.14%)	97 (46.19%)	0.845
Diabetes	68 (28.1%)	102 (32.08%)	0.311	58 (27.62%)	67 (31.9%)	0.337
Hyperlipidemia	64 (26.45%)	53 (16.67%)	***0.005***	56 (26.67%)	37 (17.62%)	***0.026***
Cardiovascular diseases	157 (64.88%)	214 (67.3%)	0.549	135 (64.29%)	140 (66.67%)	0.608
Radiotherapy	3 (1.24%)	6 (1.89%)	0.546	0 (0%)	0 (0%)	ND
Chemotherapy	42 (17.36%)	45 (14.15%)	0.3	25 (11.9%)	25 (11.9%)	1
Interferon therapy	1 (0.41%)	1 (0.31%)	0.846	0 (0.00%)	1 (0.48%)	0.317
Anti-virus therapy	1 (0.41%)	1 (0.31%)	0.846	0 (0.00%)	1 (0.48%)	0.317
Income			0.143			0.299
< NT20,000	86 (38.05%)	134 (45.27%)		70 (35.9%)	82 (40.59%)	
NT20,000-NT30,000	76 (33.63%)	78 (26.35%)		66 (33.85%)	54 (26.73%)	
≧NT30,000	64 (28.32%)	84 (28.38%)		59 (30.26%)	66 (32.67%)	
Urbanization level			0.912			0.685
1	68 (28.94%)	84 (27.27%)		59 (29.06%)	56 (27.18%)	
2	66 (28.09%)	89 (28.9%)		58 (28.57%)	67 (32.52%)	
3	101 (42.98%)	135 (43.83%)		86 (42.36%)	83 (40.29%)	

p-values were obtained by chi-square test; *p* value for age was obtained by the un-paired Student *t*-test A significant difference ($p < 0.05$) is highlighted in bold italic.
CHM, Chinese herbal medicine; N, number; ND, not determined; NT, new Taiwan dollar.
The comorbidities included hypertension (ICD-9-CM: 401–405), diabetes (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), and cardiovascular diseases (ICD-9-CM: 390–459).
These comorbidities were identified before the index date. The index date was defined as the date when the 14 CHM cumulative days were completed. Individual matching method was performed for age, gender, and chemotherapy. The duration was defined between the diagnosed date of liver cancer with surgical resection and the index date. Urbanization level 1 indicates the highest level; urbanization level 3 indicates the lowest level.

Table 2
Hazard ratios (95% CI) for overall mortality in liver cancer patients with surgical resection.

Variable	Univariate			Multivariate		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
CHM use (vs. non-CHM use)	0.59	(0.83-0.59)	***0.002***	0.58	(0.83-0.58)	***0.0025***
Comorbidities						
Hypertension (vs. no)	0.79	(1.37-0.79)	0.3973	0.86	(1.71-0.86)	0.6721
Diabetes (vs. no)	1.52	(2.64-1.52)	0.1337	1.5	(2.71-1.5)	0.1744
Hyperlipidemia (vs. no)	0.76	(1.38-0.76)	0.3672	0.87	(1.67-0.87)	0.6795
Cardiovascular diseases (vs. no)	0.66	(1.17-0.66)	0.152	0.62	(1.24-0.62)	0.1721

CHM, Chinese herbal medicine; HR, hazard ratio; 95% CI, 95% confidence interval.
Models adjusted for CHM use, and comorbidities.
A significant difference ($p < 0.05$) is highlighted in bold italic.

Taiwan National Health Research Institute and was approved by the Institutional Review Board of the China Medical University Hospital (approval number: CMUH107-REC3-074(AR-1).

2.6. Statistical analysis

Categorical data are presented as numbers and percentages and included age, gender, time from diagnosis of liver cancer with surgical resection to the index date, comorbidities, radiotherapy, chemotherapy, interferon therapy, anti-viral therapy, income, and urbanization level (Table 1).

Categorical data were evaluated using chi-squared tests. A Cox proportional hazard regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of the risk of overall mortality among patients with liver cancer who underwent surgical resection and used CHM, compared to non-CHM users after adjustment for comorbidities and the inclusion of death as a competing risk (Table 2, Table S6, and Table S**7**).

The Kaplan-Meier method and the log-rank test were used to estimate the cumulative risks of overall mortality between CHM and non-CHM users (Fig. 2, Fig. S**3, and** Table S**3**). Chinese herbal medicine usage patterns and CHM composition are shown in Table S1 and Table S2, respectively. All *p*-values less than 0.05 indicated statistically significant differences. SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for data management and statistical analyses.

3. Results

3.1. Demographic characteristics of patients with liver cancer who underwent surgical resection

The study subject identification flow chart is presented in Fig. 1. There were 1504 cases of liver cancer with surgical resection from 2000 to 2009 in Taiwan. Among these, 242 patients were assigned to CHM treatment for a cumulative period of more than 14 days within the first year of liver cancer diagnosis followed by first surgical resection. Three hundred eighteen patients assigned no CHM treatment (non-CHM users). The incidence of hyperlipidemia differed between these two groups (p-value < 0.05, Table 1). To reduce potential bias, an individual matching method was used to match individuals based on age, gender, radiotherapy, and chemotherapy.

As shown in Table 1, among the matched subjects, there were no significant differences between the matched CHM and non-CHM users, except for hyperlipidemia, which occurred more in CHM users than in non-CHM users (CHM users: 26.67%, non-CHM users: 17.62%; p-value = 0.026, Table 1).

3.2. Hazard ratio for overall mortality

A multivariate Cox proportional hazard model was used to estimate the risk of overall mortality among patients with liver cancer who underwent surgical resection (Table 2). As shown in Table 2, CHM users had a lower risk of overall mortality among patients with liver cancer who underwent surgical resection (HR: 0.57, 95% CI = 0.40-0.81; p-value = 0.0025). The 10-year cumulative incidences of overall mortality are shown as Kaplan-Meier survival plots (Fig. 2). The cumulative incidences of overall mortality were significantly lower in CHM users than in non-users (Fig. 2; log-rank test, p-value < 0.05). Chinese herbal medicine as an adjunctive therapy exerted a protective effect in patients with liver cancer who underwent surgical resection.

3.3. CHM prescription pattern in patients with liver cancer who underwent surgical resection

Chinese herbal medicine prescriptions by TCM doctors for treatment of patients with liver cancer who underwent surgical resection are listed in Table S**1**. The compositions of each herbal formula and single herbs are summarized in Table S**2**. The top 50 two-CHM combinations were used for association rule mining and network analysis (Table 3 and Fig. 3). Prescription frequency, support (%), confidence (%), and lift of the association rules were investigated (Table 3). Higher values of support, confidence, and lift represented a higher degree of association among CHM products. As shown in Table 3, for patients with liver cancer who underwent surgical resection, the CHM co-prescription pattern Ban-Zhi-Lian → Bai-Hua-She-She-Ca (frequency: 519, support: 6.8%, confidence: 84.0%, lift: 6.4) had the highest frequency, followed by Suan-Zao-Ren → Bai-Hua-She-She-Cao (frequency: 397, support: 2.8%, confidence: 45.3%, lift: 3.5).

The CHM network and core treatments prescribed to patients with liver cancer who underwent surgical resection were also investigated. As shown in Fig. 3, CHM combinations and their networks were identified. There was one main CHM cluster with Bai-Hua-She-She-Cao (BHSSC) as the core CHM, and Ban-Zhi-Lian (BZL) was also an important CHM.

4. Discussion

In this retrospective pharmacoepidemiologic study of long-term use of complementary medicines, use of CHM as an adjunctive therapy was associated with reduced overall mortality in patients with liver cancer who underwent surgical resection, as evidenced by the Cox proportional hazards model, Kaplan-Meier survival curve, and log-rank test. We then investigated the prescription patterns of CHM using

Table 3
Most commonly used pairs of CHM products for liver cancer patients with surgical resection in Taiwan.

CHM products (LHS, X)	Chinese name		CHM products (RHS, Y)	Chinese name	Frequency of prescriptions of X and Y products	Support (X) (%)	Confidence (X →Y) (%)	Lift
Ban-Zhi-Lian (BZL)	半枝蓮	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	519	6.8	84	6.4
Suan-Zao-Ren (SZR)	酸棗仁	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	397	2.8	45.3	3.5
Jia-Wei-Xiao-Yao-San (JWXYS)	加味逍遙散	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	642	2.2	21.5	1.6
Ye-Jiao-Teng (YJT)	夜交藤	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	305	1.8	37.7	2.9
Ban-Zhi-Lian (BZL)	半枝蓮	→	Jia-Wei-Xiao-Yao-San (JWXYS)	加味逍遙散	519	1.8	22	2.2
Yi-Guan-Jian (YGJ)	一貫煎	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	249	1.8	45.8	3.5
Chai-Hu-Shu-Gan-Tang (CHSGT)	柴胡疏肝湯	→	Bai-Hua-She-She-Cao (BHSSC)	白花蛇舌草	283	1.8	39.9	3.1
Suan-Zao-Ren (SZR)	酸棗仁	→	Ban-Zhi-Lian (BZL)	半枝蓮	397	1.7	27.5	3.4

CHM, Chinese herbal medicine; LHS, left-hand-side; RHS, right-hand-side.
Support (X) (%) = Frequency of prescriptions of X and Y products / total prescriptions x 100%.
Confidence (X →Y) (%) = Frequency of prescriptions of X and Y products / Frequency of prescriptions of X product x 100%.
P (Y) (%) = Frequency of prescriptions of Y product / total prescriptions x 100%.
Lift = Confidence (X →Y) (%) / P (Y) (%).

association rule mining and network analysis. Our results showed that CHM treatment was associated with reduced risk of overall mortality for patients with liver cancer who underwent surgical resection.

Patients with liver cancer who undergo surgical resection have better overall and recurrence-free survival rates than those who receive sequential treatment with only chemotherapy and radiofrequency ablation treatment.[6] In this study, we observed that patients with liver cancer who underwent surgical resection and also used CHM as an adjuvant treatment were at lower risk for overall mortality. Several Chinese herbs and related natural compounds exert anti-inflammatory, hepatoprotective, and anti-liver cancer effects.[25–27] Chinese herbs may also attenuate liver fibrosis through modulation of the TGF-β/Smad signaling pathway.[14,28] Our pharmacoepidemiologic results showed the effects of clinically-used CHM on overall mortality in patients with liver cancer who underwent surgical resection.

Chinese herbal medicine network analysis and core treatments prescribed for patients with liver cancer who underwent surgical resection suggested that Ban-Zhi-Lian → Bai-Hua-She-She-Cao had the highest overall values for frequencies, support, confidence, and lift, followed by Suan-Zao-Ren → Bai-Hua-She-She-Cao. Bai-Hua-She-She-Cao (BHSSC; *Oldenlandia diffusa (Willd.) Roxb.*, Family *Rubiaceae*) is used in Chinese medicine to treat hepatitis and liver cancer.[11,29–31] Other pharmacological activities of BHSSC have also been reported, including anti-cancer, immunomodulatory, anti-inflammatory, hepatoprotective, and anti-oxidative activities.[32–36] Ursolic acid, one of the natural components of BHSSC, suppresses growth of hepatocellular carcinoma by inhibiting the STAT3 signaling pathway.[37,38] Oleanolic acid, another natural component of BHSSC, induces cancer cell death when used in conjunction with sorafenib, a drug used to treat hepatocellular carcinoma. Oleanolic acid also protects against multi-organ toxicity induced by doxorubicin (a chemotherapy drug) during treatment of hepatocellular carcinoma.[39,40] 1,3-Dihydroxy-2-methyl anthraquinone, a natural component of BHSSC, protects against liver cancer via mitochondrial apoptotic and death receptor pathways.[31] 2-Hydroxy-3-methyl anthraquinone and 1-methoxy-2-hydroxy anthraquinone, components of BHSSC, inhibit SPC-1-A, Bcap37, and HepG2 cancer cells via the mitochondrial apoptotic pathway.[41]

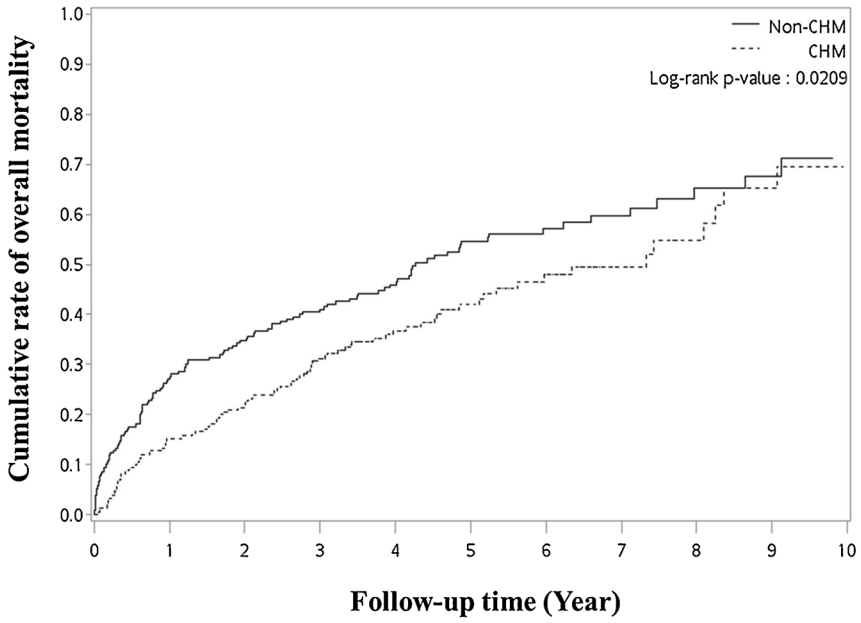
Ban-Zhi-Lian (BZL; *Scutellaria barbata D. Don*, Family *Labiatae*) has been shown to protect the liver and is used to treat hepatitis and hepatoma.[11,42,43] Other pharmacological activities of BZL include anti-cancer, immunomodulatory, and anti-inflammatory activities.[44–47] Scutellarin, a natural component of BZL, protects against diosbulbin B-induced liver injury by inhibiting NF-κB-mediated hepatitis and reducing liver injury induced by oxidative stress.[48] Scutellarin also suppresses migration and invasion of liver cancer cells and induces cancer cell apoptosis via inhibition of STAT3/Girdin/Akt activity.[49,50] Flavonoids contained in BZL induce apoptosis in hepatoma cells via the mitochondrial pathway, inhibit invasion of hepatocarcinoma via MMP/TIMP *in vitro*, and exhibit anti-angiogenic effects.[51–53]

Suan-Zao-Ren (SZR; *Ziziphus jujuba Mill.*, Family *Rhamnaceae*) is obtained from dried seeds and is used to treat insomnia.[54–56] The root bark and fruit pulp of *Ziziphus jujuba Mill.* exert hepatoprotective effects and reduce chronic inflammation.[57–59]

The strength of our study lies in the fact that the findings can be extrapolated to the general Taiwanese population because our study was based on the NHIRD in Taiwan, which is representative of the general population. There are also some limitations of this study. Factors such as diet, exercise, supportive care from families, blood biochemical data, genetic data, and compliance or adherence to medication use data could not be obtained; these are important for evaluating comorbidities.

5. Conclusion

CHM users showed significantly lower risk of mortality than non-users among patients with liver cancer who underwent surgical



Number at risk

Non-CHM users	118	57	16	13	9	13	3	2	3	1	1
CHM users	92	32	13	20	9	6	5	1	2	3	1

Fig. 2. Cumulative incidence of overall mortality between matched CHM and non-CHM users among patients with liver cancer who underwent surgical resection.

resection. In the CHM group, Ban-Zhi-Lian → Bai-Hua-She-She-Cao and Suan-Zao-Ren → Bai-Hua-She-She-Cao were the top two co-CHM prescriptions. Based on a network analysis, BHSSC and BZL were the core CHMs in the cluster. Use of CHM as an adjunctive therapy may reduce the risk of overall mortality in patients with liver cancer who underwent surgical resection. Further studies should be performed to determine the safety and efficacy of CHM use in patients with liver cancer.

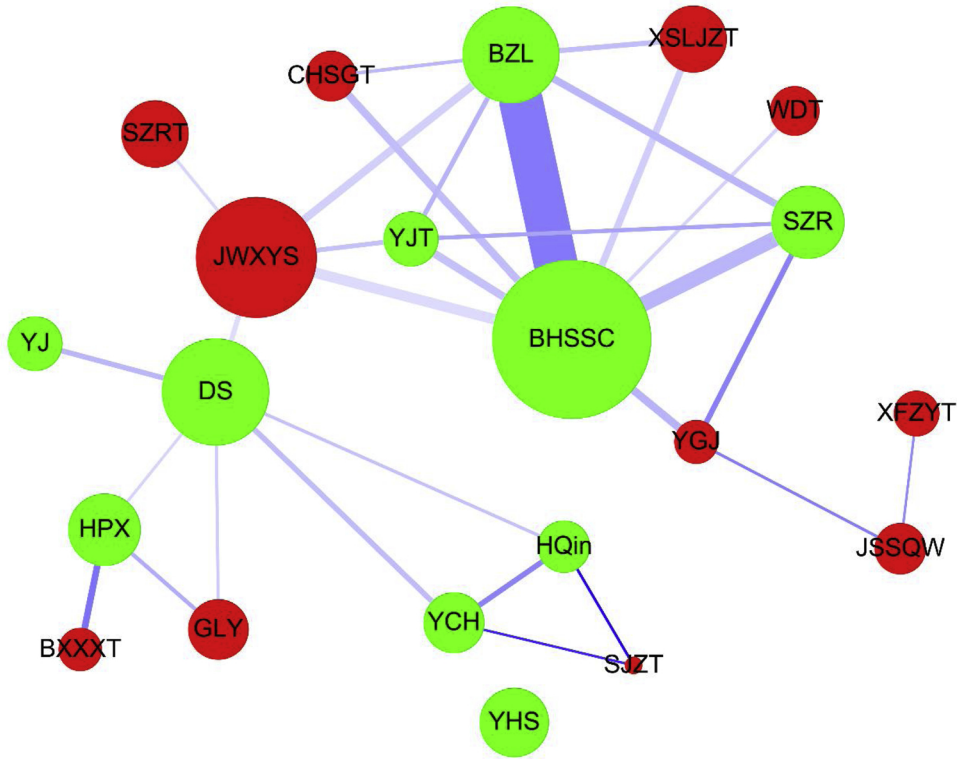


Fig. 3. Network analysis of CHM prescription patterns for patients with liver cancer who underwent surgical resection. The red circles represents herbal formulas and the green circles represents single herbs. The sizes of the circles represent the frequency of prescription for each CHM. Larger circles indicate a higher prescription frequency. Lines connecting CHMs represent support values. Thicker lines represent higher support value. Darker lines represent higher lift values. The connection between CHMs is more important when the connecting line is thicker and darker. Herbal formulas: JWXYS, Jia-Wei-Xiao-Yao-San; SZRT, Suan-Zao-Ren-Tang; XSLJZT, Xiang-Sha-Liu-Jun-Zi-Tang; GLY, Gan-Lu-Yin; JSSQW, Ji-Sheng-Shen-Qi-Wan; CHSGT, Chai-Hu-Shu-Gan-Tang; WDT, Wen-Dan-Tang; XFZYT, Xue-Fu-Zhu-Yu-Tang; YGT, Yi-Guan-Jian; BXXXT, Ban-Xia-Xie-Xin-Tang. Single herbs: BHSSC, Bai-Hua-She-She-Cao; DS, Dan-Shen; BZL, Ban-Zhi-Lian; SZR, Suan-Zao-Ren; HPX, Hai-Piao-Xiao; YHS, Yan-Hu-Suo; YCH, Yin-Chen-Hao; YJT, Ye-Jiao-Teng; YJ, Yu-Jin; HQin, Huang-Qin (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Declaration of Competing Interest

The authors declare that they have no competing interests.

Authors' contributions

XL and YJL wrote the manuscript and interpreted the data. CJC, TML, JSC, PHC, CHK, THL, CCL, and SMH collected, assembled, and analyzed the data. FJT and YJL provided study materials. WML and YJL designed, conceived the study and amended the manuscript.

Acknowledgements

This study was based entirely on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, and managed by the National Health Research Institutes. The interpretations and conclusions in this study do not represent those of the National Health Insurance Administration, Department of Health, or National Health Research Institutes. We also thank Drs. Kuan-Teh Jeang and Willy W.L. Hong for technical assistance and suggestions. This study was supported by grants from the China Medical University (CMU107-S-13 and CMU107-S-15), the China Medical University Hospital (DMR-107-042, DMR-108-113, DMR-108-114, DMR-108-118), and the Ministry of Science and Technology, Taiwan (MOST 105-2314-B-039 -037 -MY3, MOST 106-2320-B-039 -017 -MY3, and MOST 108-2314-B-039-044-MY3). The funding entities for this study had no roles in the study design, data collection, data analysis, interpretation, or authorship of this manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.102213.

References

1. Organization. *WH. World Cancer report 2014* 2014; 2014 pp. Chapter 5.6.
2. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific Region. *Gut Liver.* 2016;10(3):332–339.
3. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet.* 2016;388(10053):1459–1544.
4. Huang SF, Chang IC, Hong CC, et al. Metabolic risk factors are associated with non-hepatitis B non-hepatitis C hepatocellular carcinoma in Taiwan, an endemic area of chronic hepatitis B. *Hepatol Commun.* 2018;2(6):747–759.
5. Tsim NC, Frampton AE, Habib NA, Jiao LR. Surgical treatment for liver cancer. *World J Gastroenterol.* 2010;16(8):927–933.
6. Liu H, Wang ZG, Fu SY, et al. Randomized clinical trial of chemoembolization plus radiofrequency ablation versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. *Br J Surg.* 2016;103(4):348–356.
7. Zhou J, Sun HC, Wang Z, et al. Guidelines for diagnosis and treatment of primary liver cancer in China (2017 Edition). *Liver Cancer.* 2018;7(3):235–260.
8. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the study of liver diseases. *Hepatology.* 2018;68(2):723–750.
9. Tsai TY, Livneh H, Hung TH, Lin IH, Lu MC, Yeh CC. Associations between prescribed Chinese herbal medicine and risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide population-based cohort study. *BMJ Open.* 2017;7(1):e014571.
10. Xiong F, Guan YS. Cautiously using natural medicine to treat liver problems. *World J Gastroenterol.* 2017;23(19):3388–3395.
11. Tsai FJ, Cheng CF, Chen CJ, et al. Effects of Chinese herbal medicine therapy on survival and hepatic outcomes in patients with hepatitis C virus infection in Taiwan. *Phytomedicine.* 2018;57:30–38.
12. Hu Y, Wang S, Wu X, et al. Chinese herbal medicine-derived compounds for cancer therapy: a focus on hepatocellular carcinoma. *J Ethnopharmacol.* 2013;149(3):601–612.
13. Zhao YL, Cai GM, Hong X, Shan LM, Xiao XH. Anti-hepatitis B virus activities of triterpenoid saponin compound from Potentilla anserine L. *Phytomedicine.* 2008;15(4):253–258.
14. Liu H, Dong F, Li G, et al. Liuweiwuling tablets attenuate BDL-induced hepatic fibrosis via modulation of TGF-beta/Smad and NF-kappaB signaling pathways. *J Ethnopharmacol.* 2018;210:232–241.
15. Li Y, Martin RC. 2nd. Herbal medicine and hepatocellular carcinoma: applications and challenges. *Evid Based Complement Alternat Med.* 2011;2011:541209.
16. Xi SY, Minuk GY. Role of traditional Chinese medicine in the management of patients with hepatocellular carcinoma. *World J Hepatol.* 2018;10(11):799–806.
17. Liu ML, Chien LY, Tai CJ, Lin KC, Tai CJ. Effectiveness of traditional chinese medicine for liver protection and chemotherapy completion among Cancer patients. *Evid Based Complement Alternat Med.* 2011;2011:291843.
18. Leem J, Jung W, Kim Y, Kim B, Kim K. Exploring the combination and modular characteristics of herbs for alopecia treatment in traditional Chinese medicine: an association rule mining and network analysis study. *BMC Complement Altern Med.* 2018;18(1):204.
19. Cheng CF, Chien-Fu Lin J, Tsai FJ, et al. Protective effects and network analysis of natural compounds obtained from Radix dipsaci, Eucommiae cortex, and Rhizoma drynariae against RANKL-induced osteoclastogenesis in vitro. *J Ethnopharmacol.* 2019;244:112074.
20. Cheng CF, Lin YJ, Tsai FJ, et al. Effects of Chinese herbal medicines on the risk of overall mortality, readmission, and reoperation in hip fracture patients. *Front Pharmacol.* 2019;10:629.
21. Lin YJ, Liang WM, Chen CJ, et al. Network analysis and mechanisms of action of Chinese herb-related natural compounds in lung cancer cells. *Phytomedicine.* 2019;58:152893.
22. Tsai FJ, Cheng CF, Chen CJ, et al. Effects of Chinese herbal medicine therapy on survival and hepatic outcomes in patients with hepatitis C virus infection in Taiwan. *Phytomedicine.* 2019;57:30–38.
23. Chen HY, Lin YH, Su IH, Chen YC, Yang SH, Chen JL. Investigation on Chinese herbal medicine for primary dysmenorrhea: implication from a nationwide prescription database in Taiwan. *Complement Ther Med.* 2014;22(1):116–125.
24. Tsai FJ, Li TM, Cheng CF, et al. Effects of Chinese herbal medicine on hyperlipidemia and the risk of cardiovascular disease in HIV-infected patients in Taiwan. *J Ethnopharmacol.* 2018;219:71–80.
25. Gao Q, Yang M, Zuo Z. Overview of the anti-inflammatory effects, pharmacokinetic properties and clinical efficacies of arctigenin and arctiin from Arctium lappa L. *Acta Pharmacol Sin.* 2018;39(5):787–801.
26. Hu B, An HM, Wang SS, Chen JJ, Xu L. Preventive and therapeutic effects of chinese herbal compounds against hepatocellular carcinoma. *Molecules.* 2016;21(2):142.
27. Li H, Wang X, Liu Y, et al. Hepatoprotection and hepatotoxicity of Heshouwu, a Chinese medicinal herb: Context of the paradoxical effect. *Food Chem Toxicol.* 2017;108(Pt B):407–418.
28. Li X, He C, Wu WY, Huang H, Li WZ, Yin YY. Antifibrotic effects of Acremoniumterricola milleretal mycelium on immunological hepatic fibrosis in rats. *Mol Med Rep.* 2014;10(6):3327–3333.
29. Ting CT, Kuo CJ, Hu HY, Lee YL, Tsai TH. Prescription frequency and patterns of Chinese herbal medicine for liver cancer patients in Taiwan: A cross-sectional analysis of the National Health Insurance Research Database. *BMC Complement Altern Med.* 2017;17(1):118.
30. Chen XZ, Cao ZY, Chen TS, et al. Water extract of Hedyotis diffusa Willd suppresses proliferation of human HepG2 cells and potentiates the anticancer efficacy of low-dose 5-fluorouracil by inhibiting the CDK2-E2F1 pathway. *Oncol Rep.* 2012;28(2):742–748.
31. Li YL, Zhang J, Min D, Hongyan Z, Lin N, Li QS. Anticancer effects of 1,3-Dihydroxy-2-Methylanthraquinone and the ethyl acetate fraction of Hedyotis diffusa willd against HepG2 carcinoma cells mediated via apoptosis. *PLoS One.* 2016;11(4):e0151502.
32. Gupta S, Zhang D, Yi J, Shao J. Anticancer activities of Oldenlandia diffusa. *J Herb Pharmacother.* 2004;4(1):21–33.
33. Chen R, He J, Tong X, Tang L, Liu M. The Hedyotis diffusa Willd. (Rubiaceae): a review on phytochemistry, pharmacology, quality control and pharmacokinetics. *Molecules.* 2016;21(6).
34. Chung HS, Jeong HJ, Hong SH, et al. Induction of nitric oxide synthase by Oldenlandia diffusa in mouse peritoneal macrophages. *Biol Pharm Bull.* 2002;25(9):1142–1146.
35. Lin CC, Ng LT, Yang JJ, Hsu YF. Anti-inflammatory and hepatoprotective activity of peh-hue-juwa-chi-cao in male rats. *Am J Chin Med (Gard City N Y).* 2002;30(2–3):225–234.
36. Wang N, Li DY, Niu HY, Zhang Y, He P, Wang JH. 2-hydroxy-3-methylanthraquinone from Hedyotis diffusa Willd induces apoptosis in human leukemic U937 cells through modulation of MAPK pathways. *Arch Pharm Res.* 2013;36(6):752–758.
37. Liu T, Ma H, Shi W, et al. Inhibition of STAT3 signaling pathway by ursolic acid suppresses growth of hepatocellular carcinoma. *Int J Oncol.* 2017;51(2):555–562.
38. Wu PK, Chi Shing Tai W, Liang ZT, Zhao ZZ, Hsiao WL. Oleanolic acid isolated from Oldenlandia diffusa exhibits a unique growth inhibitory effect against ras-transformed fibroblasts. *Life Sci.* 2009;85(3–4):113–121.
39. Lange M, Abhari BA, Hinrichs TM, Fulda S, Liese J. Identification of a novel oxidative stress induced cell death by Sorafenib and oleanolic acid in human hepatocellular carcinoma cells. *Biochem Pharmacol.* 2016;118:9–17.
40. Sarfraz M, Afzal A, Raza SM, et al. Liposomal co-delivered oleanolic acid attenuates doxorubicin-induced multi-organ toxicity in hepatocellular carcinoma. *Oncotarget.* 2017;8(29):47136–47153.
41. Shi Y, Wang CH, Gong XG. Apoptosis-inducing effects of two anthraquinones from Hedyotis diffusa WILLD. *Biol Pharm Bull.* 2008;31(6):1075–1078.
42. Dai Z, Liu X, Ji Z, et al. The effect-enhancing and toxicity-reducing action of the extract of herba Scutellariae barbatae for chemotherapy in hepatoma H22 tumor-bearing mice. *J Tradit Chin Med.* 2008;28(3):205–210.
43. Lin SC, Lin CC, Lin YH, Chen CH. Protective and therapeutic effects of ban-zhi-lian on hepatotoxin-induced liver injuries. *Am J Chin Med (Gard City N Y).*

1994;22(1):29–42.
44. Zhang L, Ren B, Zhang J, et al. Anti-tumor effect of Scutellaria barbata D. Don extracts on ovarian cancer and its phytochemicals characterisation. *J Ethnopharmacol.* 2017;206:184–192.
45. Liu J, Jiang M, Li Z, et al. A novel systems pharmacology method to investigate molecular mechanisms of Scutellaria barbata D. Don for non-small cell lung cancer. *Front Pharmacol.* 2018;9:1473.
46. Xu Y, Chen XX, Jiang YX, Zhang DD. Ethyl acetate fraction from Hedyotis diffusa plus Scutellaria barbata exerts anti-inflammatory effects by regulating miR-155 expression and JNK signaling pathway. *Evid Based Complement Alternat Med.* 2018:3593408.
47. Lee SR, Kim MS, Kim S, Hwang KW, Park SY. Constituents from Scutellaria barbata inhibiting nitric oxide production in LPS-Stimulated microglial cells. *Chem Biodivers.* 2017;14(11).
48. Niu C, Sheng Y, Yang R, et al. Scutellarin protects against the liver injury induced by diosbulbin B in mice and its mechanism. *J Ethnopharmacol.* 2015;164:301–308.
49. Ke Y, Bao T, Wu X, et al. Scutellarin suppresses migration and invasion of human hepatocellular carcinoma by inhibiting the STAT3/Girdin/Akt activity. *Biochem Biophys Res Commun.* 2017;483(1):509–515.
50. Xu H, Zhang S. Scutellarin-induced apoptosis in HepG2 hepatocellular carcinoma cells via a STAT3 pathway. *Phytother Res.* 2013;27(10):1524–1528.
51. Gao J, Lu WF, Dai ZJ, et al. Induction of apoptosis by total flavonoids from Scutellaria barbata D. Don in human hepatocarcinoma MHCC97-H cells via the mitochondrial pathway. *Tumour Biol.* 2014;35(3):2549–2559.
52. Dai ZJ, Wang BF, Lu WF, et al. Total flavonoids of Scutellaria barbata inhibit invasion of hepatocarcinoma via MMP/TIMP in vitro. *Molecules.* 2013;18(1):934–950.
53. Dai ZJ, Lu WF, Gao J, et al. Anti-angiogenic effect of the total flavonoids in Scutellaria barbata D. Don. *BMC Complement Altern Med.* 2013;13:150.
54. Yeh CH, Arnold CK, Chen YH, Lai JN. Suan zao ren tang as an original treatment for sleep difficulty in climacteric women: A prospective clinical observation. *Evid Based Complement Alternat Med.* 2011;2011:673813.
55. Rodriguez Villanueva J, Rodriguez Villanueva L. Experimental and clinical pharmacology of Ziziphus jujuba mills. *Phytother Res.* 2017;31(3):347–365.
56. Shergis JL, Ni X, Sarris J, et al. Ziziphus spinosa seeds for insomnia: a review of chemistry and psychopharmacology. *Phytomedicine.* 2017;34:38–43.
57. Kandimalla R, Dash S, Kalita S, et al. Protective effect of bioactivity guided fractions of Ziziphus jujuba Mill. root bark against hepatic injury and chronic inflammation via inhibiting inflammatory markers and oxidative stress. *Front Pharmacol.* 2016;7:298.
58. Rajopadhye A, Upadhye AS. Estimation of bioactive compound, maslinic acid by HPTLC, and evaluation of hepatoprotective activity on fruit pulp of Ziziphus jujuba Mill. cultivars in India. *Evid Based Complement Alternat Med.* 2016;2016:4758734.
59. Yue Y, Wu S, Zhang H, et al. Characterization and hepatoprotective effect of polysaccharides from Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou sarcocarp. *Food Chem Toxicol.* 2014;74:76–84.