



## Retrospective Cohort Study

# Chinese herbal medicine decreases incidence of hepatocellular carcinoma in diabetes mellitus patients with regular insulin management

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## Abstract

### BACKGROUND

Type 2 diabetes mellitus (DM) is an independent risk factor for hepatocellular carcinoma (HCC), while insulin is a potent mitogen. Identifying a new therapeutic modality for preventing insulin users from developing HCC is a critical goal for researchers.

### AIM

To investigate whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control.

### METHODS

We used data acquired from the Taiwanese National Health Insurance research database between 2000 and 2017. We identified patients with DM who were prescribed insulin for > 3 months. The herb user group was further defined as patients prescribed herbal medication for DM for > 3 months per annum during

follow-up. We matched the herb users to nonusers at a 1:3 ratio according to age, sex, comorbidities and index year by propensity score matching. We analyzed HCC incidence, HCC survival rates, and the herbal prescriptions involved.

## RESULTS

We initially enrolled 657144 DM patients with regular insulin use from 2000 to 2017. Among these, 46849 patients had used a herbal treatment for DM, and 140547 patients were included as the matched control group. The baseline variables were similar between the herb users and nonusers. DM patients with regular herb use had a 12% decreased risk of HCC compared with the control group [adjusted hazard ratio (aHR) = 0.88, 95%CI = 0.80–0.97]. The cumulative incidence of HCC in the herb users was significantly lower than that of the nonusers. Patients with a herb use of > 5 years cumulatively exhibited a protective effect against development of HCC (aHR = 0.82,  $P < 0.05$ ). Of patients who developed HCC, herb users exhibited a longer survival time than nonusers (aHR = 0.78,  $P = 0.0001$ ). Additionally, we report the top 10 herbs and formulas in prescriptions and summarize the potential pharmacological effects of the constituents. Our analysis indicated that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza* Bunge (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim. (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

## CONCLUSION

This large-scale retrospective cohort study reveals that herbal medicine may decrease HCC risk by 12% in DM patients with regular insulin use.

**Key Words:** Hepatocellular carcinoma; Diabetes mellitus; Insulin; Herb; Taiwanese National health insurance research database

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**Core Tip:** Type 2 diabetes mellitus (DM) is an independent risk factor for hepatocellular carcinoma (HCC), while insulin is a potent mitogen. In this propensity-score-matched population-based cohort study, we investigated whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control. DM patients with regular herb use had a 12% decreased risk of HCC compared to the control group. The cohort with herb use of > 5 years cumulatively exhibited a protective effect against development of HCC. Moreover, among patients who developed HCC, herb users exhibited a longer survival time than non-users (adjusted hazard ratio = 0.78).

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer, and the third-leading cause of cancer-related deaths worldwide[1]. Regional incidence rates of liver cancer are the highest in East Asia [14.8 per 100000 person-years (PY)], more than double the worldwide incidence rate (7.3 per 100000 PY)[2]. This is followed by North Africa (13.2 per 100000 PY) and Southeast Asia (9.5 per 100000 PY)[2]. Treatment strategies for HCC include surgery (resection or liver transplantation), ablation, intra-arterial therapy, radiotherapy, and systemic therapy (such as tyrosine kinase inhibitor). Meanwhile, the Barcelona Clinic of Liver Cancer provides the most commonly applied staging system and guidelines regarding treatment options[3]. Major risk factors for HCC include male sex, chronic hepatitis B virus (HBV), chronic hepatitis C virus (HCV), cirrhosis, alcohol abuse, tobacco use, nonalcoholic fatty liver disease (NAFLD), diabetes mellitus (DM), obesity, and exposure to toxins such as aflatoxins and carbon tetrachloride[4]. In East Asia, chronic HBV infection is the primary risk factor for HCC; however, incidence rates of HBV infection have been decreasing following a universal vaccination policy. HCV infection is a more influential factor in Western Europe and America, where people with HCV have a 15–20-fold increased risk of developing HCC[5]. In terms of treatment, direct-acting antiviral agents have been reported to achieve a higher rate of sustained virological response (SVR) with fewer side effects compared to interferon regimens. More specifically, after treatment with direct-acting antiviral agents, HCV patients with SVR had a 78% decreased risk of HCC occurrence compared with nonresponders[6]. Henceforth, due to the declining role of viral infections, metabolic etiologies have increasingly become the focus of investigations into HCC occurrence.

Type 2 DM (T2DM) is an independent risk factor for both NAFLD and HCC[7]. It is reported that patients with T2DM have a 2.5–4-fold increased risk of developing HCC compared with normal individuals[8]. Treatments for DM include insulin-sensitizing agents, agents stimulating insulin secretion, insulin supplementation, and treatments to reduce

gastrointestinal and urinary glucose absorption. While these medications provide adequate control of blood sugar levels, some of them fail to significantly reduce the risk of HCC occurrence. In recent years, studies have demonstrated an elevated risk of HCC incidence in diabetic patients treated with insulin[9]. As insulin is a potent mitogen, it acts to upregulate various growth factors including insulin-like growth factor 1 (IGF-1), thereby increasing HCC risk[8]. As a complementary and alternative treatment option, traditional Chinese medicine (TCM) has been used for centuries in East Asia, while it has more recently been gaining popularity worldwide. Studies have reported that TCM contains many natural compounds, exerting a variety of beneficial therapeutic effects, including anticancer, and balancing blood sugar levels[10,11]. Of particular interest here, TCM indicates that *Astragalus membranaceus* (a synonym of *Astragalus propinquus*) has the effect to tonify qi. In contemporary investigations, *Astragalus membranaceus*, which is rich in antidiabetic compounds including polysaccharides, saponins and flavonoids has presented anti-HCC effects in cell lines[12,13].

Researchers have yet to report on the potential of herbal treatments to decrease HCC risk in DM patients with regular insulin use. In addition, it must be noted that the development of carcinogenesis is a long-term process. Thus, we conducted a population-based retrospective cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the potential of regular herb use to decrease HCC risk in DM patients with regular insulin management. We further analyzed the associated TCM prescriptions to provide both clinical guidance and summarize the potential molecular mechanisms of the herbs and formulas which could act to decrease HCC risk in DM patients with regular insulin management.

## MATERIALS AND METHODS

### Data source

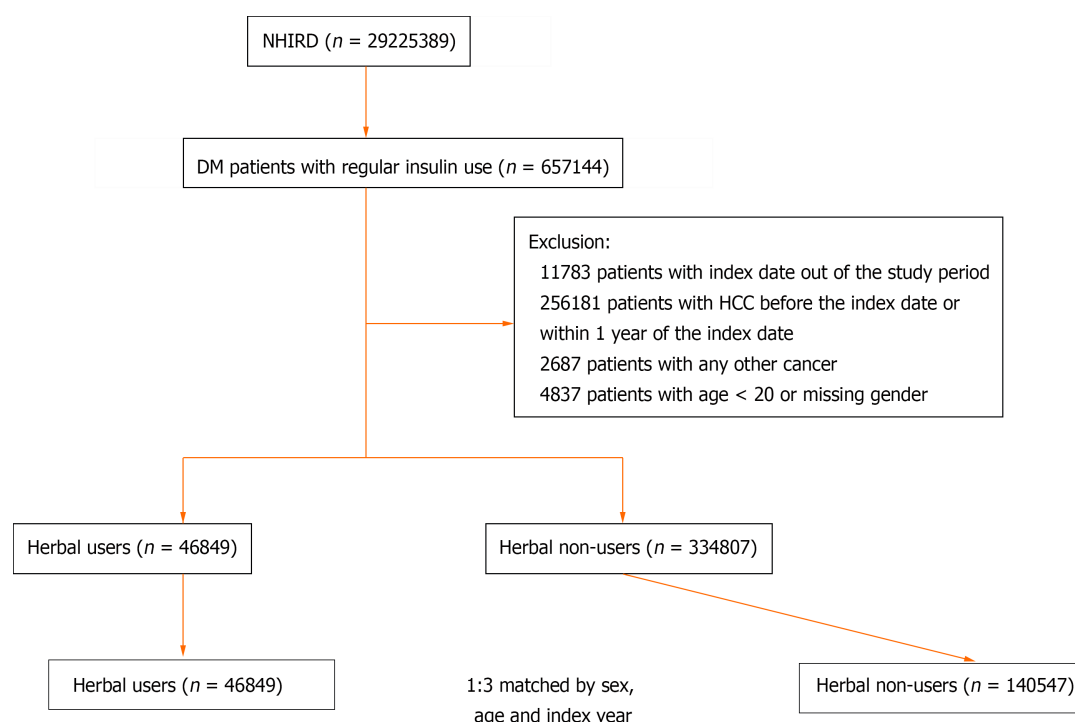
In Taiwan, over 99% of residents participate in the single-payer National Health Insurance (NHI) program, which was launched in 1995. The medical claim data are stored in the NHIRD. In addition to demographic characteristics such as sex, birth date and region of residence, the database contains critical information regarding disease diagnosis, medication usage and other treatments received. Diseases in this database are recorded using codes of the International Classification of Diseases, Ninth & Tenth Revision, Clinical Modification (ICD-9 & 10-CM). Here, we utilized the NHIRD to investigate the association between herb use and HCC in DM patients. This study was approved by the Institutional Review Board of China Medical University Hospital Research Ethics Committee, No. CMUH109-REC2-031 (CR-3). All records and personal information were anonymized prior to analysis, thus the requirement for written informed consent was waived.

### Study population and flow chart

We used data acquired from the Taiwanese NHIRD for the period January 1, 2000 to December 31, 2017. We defined subjects with three or more outpatient visits or one inpatient record of ICD-9-CM code 250 or ICD-10-CM E08-E13 as DM patients. For this cohort study, DM patients with insulin use for > 3 months were the study population. The exposure group in this study included patients with herb use due to DM for > 3 months per annum during the follow-up period. DM patients with insulin use never having received herbal treatment within the study period were defined as the nonexposure group. The index date for the exposure group was set at the first day of herb use after insulin prescription, and we assigned a random date after insulin prescription as the index date for nonexposure patients. The index date for the exposure and nonexposure groups were matched, with both post-indexed > 3 months to account for insulin exposure. Exclusion criteria included patients < 20 years old, with an index date prior to 2000 or after 2017, having any type of cancer aside from HCC, and with HCC diagnosis prior to the index date or within 1 year after the index date. We matched the herb users to nonusers at a 1:3 ratio according to age, sex, comorbidities and index year by propensity score matching. The flow chart illustrating the inclusion process in this study is shown in Figure 1.

### Main outcomes and comorbidities

The primary outcome of this study was HCC, as defined by the Registry for catastrophic illness patients. Patients with IC Cards for Severe Illness with ICD-9-CM code of 155 or ICD-10-CM code of C220, C228 were the HCC patients. Death or withdrawal from the program prior to the end of the study period (December 31, 2017) was considered as censoring. The related comorbidities included hypertension (ICD-9-CM code 401-405; ICD-10-CM code I10-I15); coronary heart disease (ICD-9-CM code 410-414; ICD-10-CM code I20-I25); ischemic stroke (ICD-9-CM code 433-434; ICD-10-CM code I63, I65, I66, I67, I68, G46.3-G46.8); hemorrhagic stroke (ICD-9-CM code 430-432; ICD-10-CM code I60, I61, I62); hyperlipidemia (ICD-9-CM code 272; ICD-10-CM code E78); renal insufficiency (ICD-9-CM code 585, 586, 588.8, 588.9; ICD-10-CM code N18, N19, N25.8, N25.9); cirrhosis (ICD-9-CM code 571.2, 571.5, 571.6; ICD-10-CM code K70.2, K70.30, K70.31, K74.0, K74.1, K74.2, K74.3, K74.4, K74.5, K74.60, K74.69); alcoholic liver damage (ICD-9-CM code 571.0, 571.1, 571.3; ICD-10-CM code K70.0, K70.10, K70.11, K70.40, K70.41, K70.0); NAFLD (ICD-9-CM code 571.8; ICD-10-CM code K74.4, K75.81, K76.0, K76.89); HBV infection (ICD-9-CM code V02.61, 070.20, 070.22, 070.30, 070.32; ICD-10-CM code Z22.51, B16.2, B16.9, B18.1, B19.10, B19.11); and HCV infection (ICD-9-CM code V02.62, 070.41, 070.44, 070.51, 070.54; ICD-10-CM code Z22.52, B17.10, B17.11, B18.2, B19.20, B19.21). In addition, several medications were included in our analysis, including lipid-lowering drugs (statins and non-statins), aspirin, HBV treatments (lamivudine, adefovir, entecavir, telbivudine, tenofovir, Peg-IFN  $\alpha$ -2a), HCV treatments (sofosbuvir, ledipasvir + sofosbuvir, velpatasvir + sofosbuvir, elbasvir + grazoprevir, glecaprevir + pibrentasvir, ombitasvir + paritaprevir + ritonavir + dasabuvir, daclatasvir, daclatasvir + asunaprevir, interferon + ribavirin), and oral antidiabetic drugs (OADs) [Biguanides, Sulfonamide, alpha glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonist, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glinides].



**Figure 1** Flow chart of study enrolment. NHIRD: National Health Insurance Research Database; HCC: Hepatocellular carcinoma; DM: Diabetes mellitus.

### Statistical analysis

For the categorical variables of baseline characteristics, we represented the number and the percentage. The mean and SD of age were presented. The differences between the two groups were shown by standard mean difference (SMD). A significant difference was shown for  $SMD > 0.1$ . We calculated the incidence rate by dividing the number of events for each 1000 PY and the hazard ratio (HR) through the Cox proportional hazard. A 95%CI and  $P$  value were also indicated. We further illustrated the cumulative incidence curve as calculated by the Kaplan-Meier method and compared by the log-rank test for statistical significance. All analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, United States). A significance level was set at  $P < 0.05$ .

## RESULTS

### Baseline characteristics and comorbidities of study participants

We enrolled 657144 DM patients with regular insulin between 2000 and 2017. Of these patients, 46849 had used herbal treatments for DM management, while 140547 were included as the matched control group. After propensity matching, the baseline variables were similar between the herb users and nonusers ( $SMD < 0.1$ ; [Table 1](#)). Nearly half of the study patients were  $> 60$  years old. The top three comorbidities identified were hyperlipidemia, hypertension, and coronary heart disease, while the proportions of all comorbidities in the study group and control group were similar. In addition, medications used by the herb users and nonusers demonstrated no differences ([Table 1](#)).

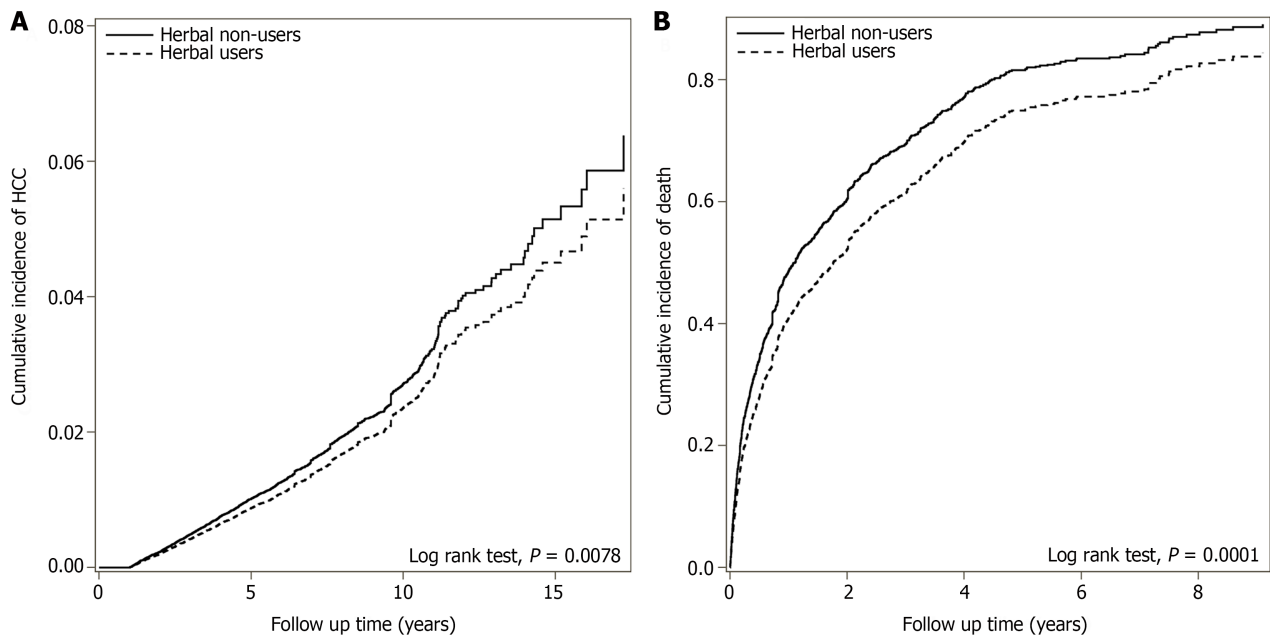
### Chinese herbal medicine decreased HCC risk among DM patients with insulin management

The association between herbal management and HCC is shown in [Table 2](#). The incidence rate of HCC among the herb users was 2.07 per 1000 PY, while it was 1.93 per 1000 PY among nonusers. After adjustment for the variables noted in [Table 1](#), the adjusted HR (aHR) of HCC was 0.88 (95%CI = 0.80–0.97;  $P = 0.001$ ) for herb users compared to the control group. As illustrated in [Figure 2A](#), the cumulative incidence of HCC in herb users was significantly lower than that of the nonusers ( $P = 0.0078$ ), while male patients had a higher risk of HCC relative to female patients (aHR = 1.77; 95%CI = 1.62–1.94;  $P < 0.001$ ). In addition, older patients exhibited an elevated risk of developing HCC. Comorbidities including cirrhosis (aHR = 4.28; 95%CI = 3.80–4.82;  $P < 0.001$ ), NAFLD (aHR = 1.24; 95%CI = 1.09–1.42;  $P < 0.001$ ), HBV infection (aHR = 2.59; 95%CI = 2.32–2.90;  $P < 0.001$ ) and HCV infection (aHR = 4.56; 95%CI = 4.09–5.08;  $P < 0.001$ ) were identified as risk factors of HCC. Similarly, patients with HBV and HCV treatments exhibited increased risks of HCC, by 3.69-fold (95%CI = 3.21–4.25;  $P < 0.001$ ) and 1.47-fold (95%CI = 1.14–1.88;  $P < 0.001$ ) respectively. Of the patients using a GLP-1 receptor agonist and SGLT2 inhibitors, the aHR of HCC was 0.40 (95%CI = 0.24–0.68;  $P < 0.001$ ) and 0.79 (95%CI = 0.64–0.98;  $P = 0.010$ ), respectively.

**Table 1** Baseline characteristics and comorbidities for herb nonusers and herb users in diabetes mellitus patients with regular insulin management in Taiwan between 2000 and 2017

Variables	DM patients with regular insulin use				SMD
	Herb non-users, <i>n</i> = 140547		Herb users, <i>n</i> = 46849		
	<i>n</i>	%	<i>n</i>	%	
Sex					0.014
Female	71872	51.14	24288	51.84	
Male	68675	48.86	22561	48.16	
Age, yr					
20-40	11623	8.27	4160	8.88	0.022
40-60	55239	39.30	18684	39.88	0.012
> 60	73685	52.43	24005	51.24	0.024
Mean (SD)	59.47 (13.25)		59.11 (13.38)		0.027
Comorbidities					
Hypertension	107255	76.31	35223	75.18	0.026
Coronary heart disease	60016	42.70	19862	42.40	0.006
Ischemic stroke	32117	22.85	10366	22.13	0.017
Hemorrhagic stroke	3418	2.43	1146	2.45	0.001
Hyperlipidemia	114028	81.13	37707	80.49	0.016
Renal insufficiency	24394	17.36	7823	16.70	0.018
Cirrhosis	4952	3.52	1847	3.94	0.022
Alcoholic liver damage	10313	7.34	3386	7.23	0.004
Nonalcoholic fatty liver disease	12398	8.82	4178	8.92	0.003
HBV infection	9560	6.80	3472	7.41	0.024
HCV infection	5770	4.11	2107	4.50	0.019
Medication					
Lipid-lowering drug					
Statin	8217	5.85	2766	5.90	0.003
Non-statin	13990	9.95	4299	9.18	0.026
Aspirin	4890	3.48	1559	3.33	0.008
HBV treatment	1947	1.39	696	1.49	0.008
HCV treatment	451	0.32	192	0.41	0.015
OAD					
Biguanides	9142	6.50	3054	6.52	0.001
Sulfonamide	8855	6.30	2914	6.22	0.003
AGI	22759	16.19	7829	16.71	0.014
Thiazolidinediones	20022	14.25	7325	15.64	0.039
DPP4 inhibitors	14313	10.18	5648	12.06	0.060
GLP-1 receptor agonist	2982	2.12	1359	2.90	0.050
SGLT2 inhibitors	8376	5.96	3639	7.77	0.072
Glinide	25298	18.00	8886	18.97	0.025
Insulin dose (mg), mean (SD)	9449.92 (135.59)		8248.88 (115.34)		0.071

AGI: -Glucosidase inhibitors; DPP4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; HBV: Hepatitis B virus; HCV: Hepatitis B virus; OAD: Oral antidiabetic agents; DM: Diabetes mellitus; SGLT2: Sodium-glucose co-transporter 2; SMD: Standard mean difference.



**Figure 2 Kaplan–Meier analysis.** A: Kaplan–Meier analysis shows lower cumulative incidence of liver cancer in regular herb users compared to nonusers in diabetes mellitus patients with insulin management during follow-up; B: Kaplan–Meier analysis shows longer survival in regular herb users compared to nonusers in diabetes mellitus patients with insulin control who had hepatocellular carcinoma in our study population. HCC: Hepatocellular carcinoma.

### Chinese herbal medicine users achieved a longer survival time compared to non-herb users among patients who developed HCC

By analyzing herb usage during the study period, patients with herb use of > 5 years cumulatively exhibited a protective effect against development of HCC (aHR = 0.82,  $P < 0.05$ ;  $P = 0.003$ ). In patients who used herbs for < 1 year, 1–2.9 years, and 3–4.9 years, the aHR of < 1 for developing HCC failed to reach statistical significance (Table 3). In the cohort of patients who developed HCC, herb users exhibited a longer survival time in days compared to non-users (aHR = 0.78,  $P = 0.0001$ ; Figure 2B).

### The top 10 herbs and formulas of prescriptions

Data regarding the top 10 single herbs and herbal formulas used by patients, and summaries of the potential pharmacological effects of the constituents are presented in Table 4. Patients with prescriptions of *Rheum palmatum* L. (Da Huang), *Salvia miltiorrhiza* Bunge (Dan Shen), *Trichosanthes kirilowii* Maxim. (Tian Hua Fen), and *Scrophularia ningpoensis* Hemsl. (Xuan Shen) exhibited lower risks of HCC, with statistical significance (aHR = 0.79–0.87;  $P < 0.05$ ). In terms of herbal formulas, patients with prescriptions of Ji Sheng Shen Qi Wan, Liu Wei Di Huang Wan, Shu Jing Huo Xie Tang, Xue Fu Zhu Yu Tang, Qi Ju Di Huang Wan, Bai Hu Jia Ren Shen Tang, and Zhi Gan Cao Tang exhibited lower risks of HCC, with an aHR 0.77–0.86, with statistical significance ( $P < 0.05$ ). The network analysis of the top 30 most prescribed herbs and formulas is presented in Figure 3. The analysis illustrates that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza* Bunge (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

## DISCUSSION

Although previous studies have demonstrated that DM patients with insulin management have an increased risk of HCC, this is the first large-scale cohort study indicating the efficacy of herbs at decreasing the HCC risk by 12% among DM patients, after adjusting for sex, age, various drug uses and major comorbidities (aHR = 0.88; 95%CI = 0.8–0.97;  $P = 0.001$ ). Furthermore, among patients who developed HCC during the study period, herbal medicine users exhibited a longer survival time in days compared to non-users (aHR = 0.78,  $P = 0.0001$ ).

Similar to previous reports, our study reveals that males had an elevated risk of developing HCC as compared to females (aHR = 1.77; 95%CI = 1.62–1.94;  $P < 0.001$ ) [14]. Additionally, approximately 50% of our cohort patients were over 60 years of age, noting that HCC risk steadily increases with age. While the diagnosed onset age of HCC varies in

**Table 2 Incidence rates of liver cancer, stratified by sex, age, comorbidities and medications, and comparing herb nonusers with herb users in diabetes mellitus patients with insulin management**

Variables	HCC			cHR	95%CI	P value	aHR <sup>1</sup>	95%CI	P value
	n	PY	IR						
Herb non-users	1487	771295	1.93	1.00	(Ref.)		1.00	(Ref.)	
Herb users	639	309158	2.07	1.04	(0.94, 1.14)	0.461	0.88	(0.80, 0.97) <sup>b</sup>	0.001
Sex									
Female	799	573926	1.39	1.00	(Ref.)		1.00	(Ref.)	
Male	1327	506527	2.62	1.93	(1.77, 2.10) <sup>c</sup>	< 0.001	1.77	(1.62, 1.94) <sup>c</sup>	< 0.001
Age, yr									
20-40	24	100697	0.24	1.00	(Ref.)		1.00	(Ref.)	
40-60	777	469199	1.66	7.01	(4.67, 10.52) <sup>c</sup>	< 0.001	5.59	(3.71, 8.40) <sup>c</sup>	< 0.001
> 60	1325	510557	2.60	11.80	(7.90, 17.73) <sup>c</sup>	< 0.001	11.19	(7.43, 16.86) <sup>c</sup>	< 0.001
Comorbidities									
Hypertension	1653	798612	2.07	1.29	(1.16, 1.43) <sup>c</sup>	< 0.001	1.10	(0.98, 1.23)	0.046
Coronary heart disease	954	443562	2.15	1.19	(1.09, 1.29) <sup>c</sup>	< 0.001	1.07	(0.97, 1.17)	0.052
Ischemic stroke	457	217351	2.10	1.14	(1.02, 1.26) <sup>a</sup>	0.016	0.98	(0.88, 1.09)	0.948
Hemorrhagic stroke	45	20459	2.20	1.21	(0.90, 1.62)	0.210	1.09	(0.81, 1.48)	0.400
Hyperlipidemia	1502	875554	1.72	0.57	(0.52, 0.62) <sup>c</sup>	< 0.001	0.67	(0.61, 0.74) <sup>c</sup>	< 0.001
Renal insufficiency	300	146465	2.05	1.15	(1.01, 1.30) <sup>a</sup>	0.030	0.92	(0.81, 1.04)	0.326
Cirrhosis	574	29944	19.17	14.20	(12.91, 15.65) <sup>c</sup>	< 0.001	4.28	(3.80, 4.82) <sup>c</sup>	< 0.001
Alcoholic liver damage	264	67522	3.91	2.24	(1.97, 2.55) <sup>c</sup>	< 0.001	1.08	(0.94, 1.25)	0.165
Nonalcoholic fatty liver disease	244	90700	2.69	1.42	(1.25, 1.63) <sup>c</sup>	< 0.001	1.24	(1.09, 1.42) <sup>b</sup>	< 0.001
HBV infection	647	68514	9.44	6.61	(6.03, 7.25) <sup>c</sup>	< 0.001	2.59	(2.32, 2.90) <sup>c</sup>	< 0.001
HCV infection	592	39215	15.10	10.60	(9.68, 11.71) <sup>c</sup>	< 0.001	4.56	(4.09, 5.08) <sup>c</sup>	< 0.001
Medication									
Lipid-lowering drug									
Statin	108	63427	1.70	0.85	(0.70, 1.04)	0.112	0.88	(0.70, 1.11)	0.313
Non-statin	169	106674	1.58	0.78	(0.67, 0.92) <sup>b</sup>	0.002	0.86	(0.73, 1.01)	0.124
Aspirin	64	35231	1.82	0.93	(0.73, 1.20)	0.590	0.75	(0.56, 1.01)	0.050
HBV treatment	324	13557	23.90	14.70	(13.05, 16.54) <sup>c</sup>	< 0.001	3.69	(3.21, 4.25) <sup>c</sup>	< 0.001
HCV treatment	71	3899	18.21	9.20	(7.26, 11.66) <sup>c</sup>	< 0.001	1.47	(1.14, 1.88) <sup>b</sup>	0.012
OAD									
Biguanides	168	68930	2.44	1.27	(1.08, 1.48) <sup>b</sup>	0.003	1.16	(0.84, 1.61)	0.368
Sulfonamide	166	66481	2.50	1.30	(1.11, 1.52) <sup>b</sup>	0.001	1.08	(0.78, 1.50)	0.676
AGI	379	175908	2.15	1.12	(1.00, 1.25)	0.052	0.93	(0.83, 1.06)	0.475
Thiazolidinediones	344	161421	2.13	1.09	(0.97, 1.23)	0.134	1.07	(0.95, 1.21)	0.197
DPP4 inhibitors	289	119437	2.42	1.26	(1.11, 1.42) <sup>c</sup>	< 0.001	1.15	(0.99, 1.32)	0.085
GLP-1 receptor agonist	14	27416	0.51	0.25	(0.15, 0.42) <sup>c</sup>	< 0.001	0.40	(0.24, 0.68) <sup>c</sup>	< 0.001
SGLT2 inhibitors	88	76062	1.16	0.56	(0.45, 0.69) <sup>c</sup>	< 0.001	0.79	(0.64, 0.98) <sup>a</sup>	0.010
Glinide	418	195582	2.14	1.11	(1.00, 1.24)	0.051	0.93	(0.82, 1.04)	0.222

<sup>a</sup>P < 0.05.

<sup>b</sup>*P* < 0.01.<sup>c</sup>*P* < 0.001.<sup>1</sup>adjusted by variables in Table 1.

AGI: -Glucosidase inhibitors; aHR: Adjusted hazard ratio; cHR: Crude hazard ratio; DPP4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis B virus; IR: Incidence rate per 1000 person-years; N: Number of events; OAD: Oral antidiabetic agents; PY: Person-years; SGLT2: Sodium-glucose co-transporter 2.

**Table 3 Risk of hepatocellular carcinoma stratified by the duration of herb use compared with nonherb use**

Variables	HCC			cHR	95%CI	<i>P</i> value	aHR <sup>1</sup>	95%CI	<i>P</i> value
	<i>n</i>	PY	IR						
Herb non-users	1487	771295	1.93	1.00	(Ref.)		1.00	(Ref.)	
Herb users									
< 1 yr	181	89349	2.03	1.04	(0.89, 1.22)	0.610	0.88	(0.76, 1.03)	0.074
1-2.9 yr	171	81924	2.09	1.05	(0.9, 1.24)	0.514	0.92	(0.78, 1.08)	0.169
3-4.9 yr	87	39932	2.18	1.09	(0.88, 1.35)	0.450	0.94	(0.76, 1.17)	0.436
≥ 5 yr	200	97953	2.04	0.99	(0.86, 1.15)	0.943	0.82	(0.71, 0.95) <sup>a</sup>	0.003

<sup>a</sup>*P* < 0.05.<sup>1</sup>adjusted by variables in Table 1.

AHR: Adjusted hazard ratio; cHR: Crude hazard ratio; HCC: Hepatocellular carcinoma; IR: Incidence rate per 1000 person-years; *n*: Number of events; PY: Person-years.

different parts of the world, Yang *et al*[4] reported a median onset age above 60 years[4], which is similar to our findings. Our stratified analysis revealed that cirrhosis patients had the highest risk of developing HCC compared to other comorbidities (aHR = 4.28; 95%CI = 3.8–4.82; *P* < 0.001). A study by Fattovich *et al*[15] reported a fourfold elevated risk of developing HCC in cirrhosis patients compared to those with chronic hepatitis[15]. With viral infection or alcohol intake, a damaged liver will undergo regeneration and tissue recovery. The repeated hepatocyte and hepatic stellate cellular proliferation may trigger cancer-related fibroblasts and lead to cirrhosis as well as HCC proliferation[16]. Furthermore, between 15% and 30% of cirrhosis patients develop T2DM due to perturbed glucose utilization and decreased insulin removal by the liver[17]. Hyperglycemia and hyperinsulinemia status may also result in development of HCC. Of note, our study identified HBV and HCV infections as major risk factors of developing HCC. The worldwide incidence of HCV-related HCC is 12–17 per 1000 PY, which is similar to our finding (15.10 per 1000 PY)[5], and the incidence of HBV-related HCC varies by region[15]. In our study, HBV and HCV treatments were adopted in accordance with patient preference and following NHI payment guidelines. HBV treatments were covered for patients with HBV DNA ≥ 2000IU/mL with five-fold elevated liver enzymes or decompensated liver status, while HCV treatments were covered for patients positive for anti-HCV for > 6 months with cirrhosis ≥ F2 or positive for HCV RNA. We hypothesize that the liver status of patients in the HBV and HCV treatment groups were generally more severe, thus causing the elevated risk of HCC incidence noted in our study.

DM is a metabolic disorder associated with hyperglycemia, hyperinsulinemia and insulin resistance. Due to metabolic disturbances, DM is noted as an independent risk factor for various types of cancer, including breast, colorectal, endometrial, pancreatic, gallbladder, renal, and liver cancers[18]. It has been reported that T2DM patients have a 2.5–4-fold risk of developing HCC compared with normal individuals[8]; the possible underlying mechanism of which is associated with insulin resistance related to hyperinsulinemia. Hyperinsulinemia increases IGF-1, causing IGF-1 and insulin receptor substrate-1 overexpression, thereby activating hepatoma cell proliferation[19]. Insulin supplementation is indicated in T2DM and gestational DM patients; however, although insulin supplements can achieve satisfactory control of blood sugar levels, mounting evidence suggests an elevated risk of HCC in diabetic patients. According to a previous study, both higher daily insulin dosage and longer treatment duration increase the risk of HCC in patients treated with insulin by adjusted odds ratio from 1.9 to 3.73[8]. More specifically, sulfonylureas, which promote insulin secretion, pose a 2.6-fold increased risk of developing HCC[20]. Our report reveals a similar result whereby sulfonylureas increased HCC risk (aHR = 1.08), but without statistical significance.

The biguanide metformin is an oral antihyperglycemic agent that has been identified as a potential hepatoprotective drug against HCC development[21]. Metformin activates adenosine monophosphate-activated protein kinase and inhibits the downstream mammalian target of rapamycin pathway, which plays a key role in preventing hepatocarcinogenesis[22]. Indeed, previous studies have reported a metformin treatment group with a 43%–76% reduced risk of HCC and reduced overall mortality risk[8,9]; however, our subgroup analysis showed no difference between biguanides users and nonusers (aHR = 1.16; 95%CI = 0.84–1.61; *P* = 0.368). Meanwhile, GLP-1 is an insulin secretagogue that ameliorates liver fat accumulation and the inflammatory microenvironment, acting to prevent NAFLD progression to nonalcoholic steatohepatitis (NASH). In our study, GLP-1 receptor agonists decreased HCC risk (aHR = 0.4; 95%CI = 0.24–0.68; *P* < 0.001).

Table 4 Possible pharmacological effects of the ingredients in the top 10 herbs and formulas

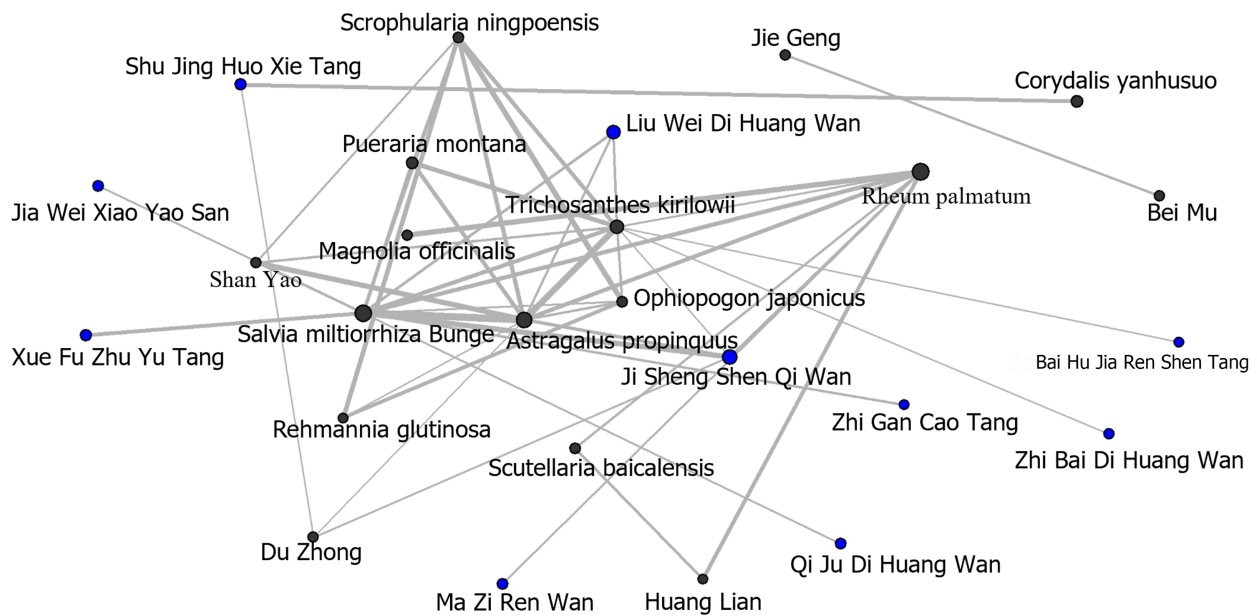
	Possible pharmacological effects of the ingredients	Average daily dose (g)	No. of persons-dosage	Frequency (%)	aHR <sup>†</sup>	95%CI	P value
Single Herbs: Pin-yin name/ Latin name					1.00	(Ref.)	
Da Huang/ <i>Rheum palmatum L</i>	Reduces oxidative stress, inhibits β-cell apoptosis and improves β-cell function[28]; Activates AMP-Activated Protein Kinase and improves glucose tolerance[37]; Ameliorates insulin resistance <i>via</i> reducing FATP1-mediated skeletal muscle lipid accumulation[38]; Inhibits HCC <i>via</i> inhibiting STAT 3 signaling pathway[39]	1	1060286	109102 (15.25)	0.83	(0.7, 0.98) <sup>a</sup>	0.013
Dan Shen/ <i>Salvia miltiorrhiza Bunge</i>	Reduces oxidative stress and inhibits apoptosis and inflammation <i>via</i> the regulation of Wnt/β-catenin, TSP-1/TGF-β1/STAT3, JNK/PI3K/ Akt, TGF-β1/NF-κB, AMPK/ ACC, signaling pathways in DM model[40]. Inhibits IGF-1[31,32]. Inhibits HCC <i>via</i> modulating PI3K/ Akt, MAPK and JAK/STAT3 signaling pathways[41]	1.9	2162061	107301 (15.00)	0.87	(0.76, 1.00) <sup>a</sup>	0.0123
Huang Qi/ <i>Astragalus propinquus</i>	Protects pancreatic β cells from apoptotic death[29]. Regulates resistin (an insulin-resistance protein)[29]. Ameliorates insulin resistance[42]. Induces apoptosis in HCC <i>via</i> decreasing the expression of Notch 1[43]. Inhibits HCC <i>via</i> repression of M2 polarization of tumor-associated macrophages [44]	2.2	2188885	94799 (13.25)	0.87	(0.75, 1.01)	0.0183
Tian Hua Fen/ <i>Trichosanthes kirilowii Maxim</i>	Ameliorates insulin resistance <i>via</i> decreasing the expression of PTGS2, NF-κB, JNK, and AKT[45]. Stimulates insulin receptor kinase activity and enhances glucose clearance[46]. Inhibits HCC cell proliferation <i>via</i> blocking PKM2-dependent glycolysis[47]	2.2	1787396	77376 (10.81)	0.83	(0.71, 0.97) <sup>a</sup>	0.0027
Yan Hu Suo/ <i>Corydalis yanhusuo</i>	Induces autophagy in HCC <i>via</i> activating the AMPK-mTOR-ULK1 and the ROS-JNK-ATG cascade and impairing the ERK/ AKT signaling pathway [26]	1.8	925275	62808 (8.78)	0.89	(0.77, 1.03)	0.0496
Ge Gen/ <i>Pueraria montana var. lobata</i>	Elevates insulin expression and enhances insulin sensitivity index[48]. Ameliorates insulin resistance[49]. Inhibits HCC invasion and metastasis <i>via</i> miR-21-mediated PTEN/ AKT signaling pathway[50]	1.8	1032475	62061 (8.67)	0.86	(0.73, 1.00)	0.0128
Xuan Shen/ <i>Scrophularia ningpoensis Hemsl</i>	Improves insulin sensitivity <i>via</i> AMPK-mediated NLRP3 inflammasome inhibition[51,52]	2.2	1099700	52418 (7.33)	0.79	(0.67, 0.94) <sup>b</sup>	0.002
Huang Chin/ <i>Scutellaria baicalensis Georgi</i>	Regulates IGF-1R/ AKT signaling pathway[53]. Ameliorates insulin resistance <i>via</i> inhibiting macrophage-mediated inflammation[54]. Elevates AMPK expression[34]. Modulates gut microbiota[34]. Inhibits HCC <i>via</i> affecting p53 signal pathway, MAPK signal pathway, apoptosis pathway, T cell receptor pathway, and macrophage-mediated tumor immunity[55]	1.9	852156	50546 (7.06)	0.93	(0.80, 1.09)	0.2098
Mai Men Dong/ <i>Ophiopogon japonicus (Thunb.) Ker Gawl</i>	Ameliorates insulin resistance <i>via</i> InsR/IRS-1/PI3K/ Akt/GSK-3/ Glut-4 signalling pathway[56]. Modulates gut microbiota[35]. Inhibits HCC <i>via</i> downregulating PTP1B expression, thereby inactivating the PI3K/ AKT pathway and activating the AMPK pathway[57]	2.3	1064080	49974 (6.98)	0.88	(0.75, 1.04)	0.0429

Hou Po/ <i>Magnolia officinalis</i>	Decreases IGF-1 and IGFBP-5[33]. Protects pancreatic $\beta$ -cells[30]. Inhibits HCC <i>via</i> AKT inhibition[58]	2.1	946453	49148 (6.87)	0.84	(0.70, 1.01)	0.0232
Herbal Formula: Pin-yin name/Latin name							
Ji Sheng Shen Qi Wan	Ameliorates insulin resistance[59]. Inhibits HCC development[60]	6.9	6239325	87687 (15.62)	0.82	(0.71, 0.96) <sup>a</sup>	0.0026
Liu Wei Di Huang Wan	Ameliorates insulin resistance <i>via</i> antioxidative effect and suppressing inflammation[61]. Induces apoptosis in HCC[62]	8.6	6803688	78029 (13.90)	0.83	(0.72, 0.96) <sup>a</sup>	0.0022
Shu Jing Huo Xie Tang	Ameliorates insulin resistance[63]. Inhibits HCC <i>via</i> regulating iron metabolism[64]	7.8	3550686	56106 (10.00)	0.86	(0.74, 1.00) <sup>a</sup>	0.0152
Xue Fu Zhu Yu Tang	Ameliorates insulin resistance, inflammation and oxidative stress[65]. Inhibits angiogenesis in HCC <i>via</i> blocking ERK/MAPK and NF- $\kappa$ B signalling pathway[66]	6.4	3466030	55091 (9.81)	0.80	(0.68, 0.94) <sup>b</sup>	0.0025
Jia Wei Xiao Yao San	Ameliorates insulin resistance[67]. Induces apoptosis in HCC[68]. Inhibits invasion and metastasis in HCC[69]	7.7	3823372	51350 (9.15)	0.92	(0.78, 1.08)	0.1529
Qi Ju Di Huang Wan	Ameliorates insulin resistance[70]. Modulates gut microbiota[71]. Inhibits HCC <i>via</i> inducing p53-mediated apoptosis and inhibiting proliferation[62]	7.7	4309801	50271 (8.96)	0.83	(0.68, 1.00) <sup>a</sup>	0.0219
Ma Zi Ren Wan	Reduces oxidative stress, inhibits $\beta$ -cell apoptosis and improves $\beta$ -cell function[28]. Inhibits HCC <i>via</i> AKT inhibition[58]	5	2609093	50100 (8.93)	0.87	(0.70, 1.08)	0.1288
Zhi Bai Di Huang Wan	Ameliorates insulin resistance <i>via</i> IRS-1/PI3K/AKT pathway[72]. Modulates gut microbiota[36]. Induces autophagy and apoptosis in HCC [27]	7.1	3557458	46284 (8.25)	1.05	(0.89, 1.23)	0.9271
Bai Hu Jia Ren Shen Tang	Inhibits IGF-1R/Akt pathway[73]. Ameliorates insulin resistance[74,75]. Induces apoptosis in HCC[76]	8.4	4051247	43451 (7.74)	0.79	(0.65, 0.96) <sup>a</sup>	0.0043
Zhi Gan Cao Tang	Decreases blood glucose[77]; Ameliorates insulin resistance[77]; Induces apoptosis and inhibits proliferation in HCC <i>via</i> blocking PI3K/AKT signal pathway[78]	5.9	2423303	42951 (7.65)	0.77	(0.63, 0.93) <sup>b</sup>	0.0042

<sup>a</sup> $P < 0.05$ .<sup>b</sup> $P < 0.01$ .<sup>1</sup>adjusted by variables in Table 1.

ACC: Acetyl-CoA carboxylase; aHR: Adjusted hazard ratio; AMP: Adenosine monophosphate; AMPK: Adenosine monophosphate-activated protein kinase; ERK: Extracellular signal-regulated kinase; FATP1: Fatty acid transport protein 1; GLUT-4: Glucose transporter type 4; IGF-1: Insulin-like growth factor 1; IGFBP-5: Insulin-like growth factor binding protein-5; IRS-1: Insulin receptor substrate 1; JAK: Janus-activated kinase; JNK: C-Jun N-terminal kinases; MAPK: Mitogen-activated protein kinase; mTOR: Mammalian target of rapamycin; NF- $\kappa$ B: Nuclear factor kappa B; NLRP3: NLR family pyrin domain containing 3; Notch 1: Neurogenic locus notch homolog protein 1; PI3K: Phosphatidylinositol-3-kinase; PKM2: Pyruvate kinase M2; PTEN: Phosphatase and tensin homolog; PTGS2: Prostaglandin-endoperoxide synthase 2; PTP1B: Protein-tyrosine phosphatase 1B; ROS: Reactive oxygen species; STAT3: Signal transducer and activator of transcription 3; TGF- $\beta$ 1: Transforming growth factor beta-1; TSP1: Thrombospondin-1; ULK1: Unc-51-like kinase 1; HCC: Hepatocellular carcinoma; DM: Diabetes mellitus.

Previous studies have demonstrated that GLP-1 receptor agonists induce autophagy *via* elevating the transforming growth factor 1 level and reducing migration *via* suppression of the stress-activated protein kinase/c-Jun N-terminal kinase pathway[23,24], which is further supported by our findings. However, it should be noted that GLP-1 receptor agonists elevate the insulin level in patients, thereby potentially elevating the risk of HCC. Thus, more high-quality



**Figure 3 Network analysis of the top thirty most prescribed herbs and formulas.** The spot size indicates the frequency of Chinese herbal product prescription, and the line width indicates the combination frequency between two Chinese herbal products.

clinical evidence is required to clarify the association between GLP-1 receptor agonist and HCC occurrence. In addition, SGLT2 inhibitors are a new class of OAD which act to decrease glucose reabsorption in the renal proximal tubules. SGLT2 has been shown to attenuate the development of NASH and induce cell cycle arrest and apoptosis in an animal model [25]. Our report reveals a decreased HCC risk (aHR = 0.79; 95%CI = 0.64–0.98;  $P = 0.010$ ) in SGLT2 inhibitor users; however, there is a lack of clinical data regarding SGLT2 inhibitors as a protector or inducer of carcinogenesis.

Although many OADs have been developed, insulin continues to play a prominent role in the clinical setting as it is applied to such conditions as chronic DM, type 1 DM, chronic kidney disease, and gestational DM. Thus, identifying a new therapeutic modality is critical to preventing insulin users from developing HCC. As such, many of the herbs applied in TCM contain natural compounds which have been demonstrated to exert both anticancer and antidiabetic effects without causing hyperinsulinemia[10,11]. Table 4 lists and summarizes the possible pharmacological effects of the 10 most-prescribed herbs and formulas identified in our study. Importantly, previous studies have indicated that these herbs and formulas contain active compounds involved in the inhibition of HCC progression. Most of them have been shown to induce apoptosis both *in vivo* and *in vitro* in HCC cell line studies, while *Corydalis yanhusuo*[26] and *Anemarrhena asphodeloides*[27] (present in Zhi Bai Di Huang Wan and Bai Hu Jia Ren Shen Tang) have been noted to induce autophagy. In addition, *Pueraria montana* and *Paeonia lactiflora* (present in Jia Wei Xiao Yao San and Ma Zi Ren Wan) inhibit HCC invasion and metastasis. Aside from *Corydalis yanhusuo*, the other top 10 herbs and formulas have been reported to exert antidiabetic effects, primarily by ameliorating insulin resistance *via* various molecular pathways. As previously reported, *Rheum palmatum*[28], *Astragalus propinquus*[29] and *Magnolia officinalis*[30] prevent pancreatic  $\beta$ -cell death and control blood sugar levels. *Salvia miltiorrhiza*[31,32] and *Magnolia officinalis*[33] inhibit IGF-1, a tumor carcinogen, indicating their potential to inhibit HCC proliferation. Furthermore, *Scutellaria baicalensis*[34], *Ophiopogon japonicus*[35] and *Anemarrhena asphodeloides*[36] have been demonstrated to modulate gut microbiota in high-fat-diet animal models. Collectively, the present study and previous investigations indicate that the herbs identified herein are associated with both anticancer and antidiabetic effects without causing hyperinsulinemia, although further investigation is warranted.

The NHIRD used in this study provides a large sample size, covering over 99% of Taiwan's residents with a low loss of follow-up, and provides sufficient power for subgroup analyses to demonstrate convincing outcomes after adjusting for potential confounding factors. However, several limitations need to be considered. First, the NHIRD does not offer information on potential confounding factors such as body mass index, environmental/chemical exposure, alcohol/tobacco consumption, or history of family illness. Thus, we have attempted to adjust for the alcohol confounding factor by considering alcoholic liver disease, revealing no statistical significance between the two cohorts. Second, clinical data were lacking in terms of laboratory data and imaging results, making it difficult to investigate the quality of DM control, and stages of cirrhosis and HCC. Among the demographic characteristics in our patients, the proportion with cirrhosis, alcoholic liver damage and HBV/HCV infection were not significantly different between the groups, suggesting that the background risk of liver cancer occurrence was likely similar for both groups. Third, the NHIRD only records herbal prescriptions manufactured by good-manufacturing-practice-certified pharmaceutical companies; hence, herbs purchased outside of the NHI program were not analyzed in this study. However, self-paid herbs are relatively expensive, at approximately \$300 to \$400 per month, while we identified patients with > 3 months of herbal prescriptions per annum during the study period; thus, the chance of patients purchasing herbs not covered by NHI should be minimal. Fourth, due to the nature of retrospective cohort studies, bias may exist in our results. More specifically, it is reasonable to suggest that patients with a longer survival time may have received herbal treatment for a correspondingly longer period, thus warranting a prospective study to confirm our results. To minimize these limitations, we defined only patients with

long-term (> 3 months) use of insulin and herbs, and patients diagnosed with HCC according to the Registry for Catastrophic Illness Database. We also reviewed the possible mechanisms underlying herbal effects on both anti-HCC and reversal of insulin resistance to bridge our results. Our study reveals several notable findings, while the prescription patterns identified in this large-scale cohort study provide valuable clinical guidance, and warrant further clinical studies and pharmacological investigation.

## CONCLUSION

As DM patients using insulin have an increased risk of developing HCC, identifying a new therapeutic modality to prevent or mitigate this risk is of importance. This is the first large-scale cohort study to reveal that regular herbal medicine prescriptions can decrease the risk of HCC in DM patients using insulin. Herbal prescriptions may extend the survival time for DM patients with HCC. Future large-scale cohort studies or prospective studies are recommended to further support our results.

## ARTICLE HIGHLIGHTS

### Research background

Hepatocellular carcinoma (HCC) is the fifth most commonly occurring cancer globally. Type 2 diabetes mellitus (DM) is independent risk factor for HCC, while insulin is a potent mitogen. Identifying a new therapeutic modality for preventing insulin users from developing HCC is a critical goal for researchers.

### Research motivation

Previous reports have indicated the potential of herbal treatments to decrease HCC risk in DM patients. However, carcinogenesis is a long-term process. Thus, we conducted a population-based retrospective cohort study using data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate the potential of regular herb use to decrease HCC risk in DM patients with regular insulin management.

### Research objectives

The objective of this study was to evaluate whether regular herbal medicine use can decrease HCC risk in DM patients with regular insulin control.

### Research methods

We used data acquired from the Taiwanese NHIRD between 2000 and 2017. We identified patients with DM who were prescribed insulin for > 3 months. The herb group was further defined as patients prescribed herbal medication for DM for > 3 months per annum during follow-up. We analyzed HCC incidence, HCC survival rates, and the herbal prescriptions involved.

### Research results

We enrolled 657144 DM patients with regular insulin use from 2000 to 2017. Among these, 46849 patients had used herbal treatment for DM, and 140547 patients were included as the matched control group. The baseline variables were similar between the herb users and nonusers. DM patients with regular herb use had a 12% decreased risk of HCC compared to the control group. The cumulative incidence of HCC in herb users was significantly lower than that of the nonusers. Patients with herb use for > 5 years cumulatively exhibited a protective effect against development of HCC. Of patients who developed HCC, herb users exhibited a longer survival time than nonusers. Our analysis indicated that *Astragalus propinquus* (Huang Qi) plus *Salvia miltiorrhiza* Bunge (Dan Shen), and *Astragalus propinquus* (Huang Qi) plus *Trichosanthes kirilowii* Maxim (Tian Hua Fen) were the most frequent combination of single herbs. Meanwhile, Ji Sheng Shen Qi Wan plus Dan Shen was the most frequent combination of herbs and formulas.

### Research conclusions

This large-scale retrospective cohort study reveals that herbal medicine may decrease HCC risk by 12% in DM patients with regular insulin use. Furthermore, herbal prescriptions may extend the survival time for those DM patients who develop HCC.

### Research perspectives

Since herbal prescriptions are relatively cheap and commonly used, large-scale cohort studies or prospective studies are required to support our results.

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**Author contributions:** Lai HC contributed to conceptualization, methodology, writing - original draft; Cheng JC contributed to resources, investigation, validation, editing; Yip HT contributed to software, formal analysis, visualization; Jeng LB contributed to resources, supervision, editing; Huang ST contributed to methodology, writing-reviewing and editing, project administration, funding acquisition.

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