Journal of Ethnopharmacology 202 (2017) 225–233

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

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

The use of Chinese herbal medicine as an adjuvant therapy to reduce incidence of chronic hepatitis in colon cancer patients: A Taiwanese population-based cohort study

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ARTICLE INFO

Keywords:
Chinese herb medicine
Chronic hepatitis
Colon cancer, Cohort study

ABSTRACT

Ethnopharmacological relevance: There is a decided lack of in-depth studies to evaluate the effectiveness of Chinese Herbal Medicine (CHM) as an adjuvant therapy on the incidence of chronic hepatitis in patients with colon cancer.

Aim of the study: The aim of this study is to assess whether CHM treatment decreased the incidence of chronic hepatitis in colon cancer patients who received conventional Western medical treatment.

Materials and methods: A Taiwanese nationwide population-based study of colon cancer patients receiving Western medicine treatment in conjunction with CHM treatment, using data provided by the National Health Insurance (NHI) Research Database, was conducted. A total of 61676 patients were diagnosed with colon cancer in Taiwan within the defined study period, from 1997 to 2010. After randomly equal matching for age, sex, excluding patients younger than 18 years of age, chronic hepatitis before colon cancer diagnosis date, receiving acupuncture and/or moxibustion and taking CHM for less than 30 days, data from 155 patients were analyzed. Hazard ratios of incidence rate of chronic hepatitis were used to determine the influence of CHM and the therapeutic potential of herbal products in treating patients with colon cancer.

Results: CHM used for patients with colon cancer exhibited significantly decreased incidence rates of chronic hepatitis [hazard ratio (HR)=0.53; 95% confidence interval (CI):0.38–0.74], with multivariate adjustment, compared to those without CHM use. The protective effect of CHM treatment with statistical significance across the stratification of age, gender, co-morbidity and treatment modality was noted. The cumulative incidence of chronic hepatitis was also reduced in patients with colon cancer receiving CHM treatment during a five-year period. In this study, we provide the ten most used single herbs and herbal formulas that were prescribed for patients with colon cancer; moreover, we identify the eight single herbs and five formulas used in CHM treatment which significantly decreased incidence of chronic hepatitis among colon cancer patients.

Conclusions: This nationwide retrospective cohort study determined that therapy using CHM as an adjuvant modality may have a significant impact on liver protection in patients with colon cancer.

1. Introduction

In recent decades, cancer has emerged as a leading cause of death globally, involving abnormal cell growth with the potential for metastasis to other parts of the body. Colon cancer is the third most commonly diagnosed cancer in males and the second in females, with

Abbreviations: CHM, Chinese Herbal Medicine; NHI, National Health Insurance; HR, hazard ratio; CI, confidence interval; 5-FU, 5-flourouracil; GMP, Good Manufacturing Practice; NHIRD, National Health Insurance Research Database; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; P-gp, P-glycoprotein; LC3, microtubule-associated protein light chain 3S

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http://dx.doi.org/10.1016/j.jep.2017.03.027
Received 14 January 2017; Received in revised form 13 March 2017; Accepted 17 March 2017
Available online 19 March 2017
0378-8741/

an estimated 1.4 million cases and 693,900 deaths occurring in 2012 (Torre et al., 2015). Currently, the 5-year overall survival rate remains at about 60% (Moghimi-Dehkordi and Safaee, 2012). While 25% of patients are diagnosed as having colorectal cancer with metastases initially, nearly 50% of patients will develop metastases, leading to the high rates of mortality (Van Cutsem et al., 2014). Conventional treatments of colorectal cancer include surgery, radiation, and chemotherapy. The favored treatment is complete surgical removal of localized tumor, in addition to chemotherapy in patients with nearby lymph node invasion or distal metastasis. Previous studies have demonstrated that the 12.5% of patients with unresectable colon cancer with liver metastasis are associated with an improved survival rate by liver surgery after chemotherapy (Adam et al., 2004; Lam et al., 2012). Most often, 5-flourouracil (5-FU) has been used to treat advanced colon cancer since the 1990s (Laufman et al., 1987). The cytotoxic agents, such as oxaliplatin and irinotecan, were added on the standard regimens for chemotherapy: 5-FU/leucovorin/oxaliplatin or 5-FU/leucovorin/irinotecan (McWhirter et al., 2013). The combined regimens gave significantly higher treatment response rates, limitation of cancer progression, and longer survival periods (Douillard et al., 2000). Even for patients with metastatic colon cancer for whom 5-FU treatment failed, irinotecan could also have anticancer effects, including longer survival periods, fewer tumor-related symptoms, and a generally improved quality of life (Cunningham et al., 1998). While chemotherapy possesses benefits for advanced colon cancers, drug-induced hepatotoxicity has continued to be noted as a serious condition resulting from such treatment (McWhirter et al., 2013). For instance, 5-FU has been reported to increase hepatocyte steatosis via impaired β-oxidation and accumulation of fatty acids associated with increased post-operative infection. Irinotecan is often associated with steatohepatitis via mitochondrial impairment, leading to impaired β-oxidation and inflammation secondary to cytokine release. The patients with steatohepatitis had an increased risk of 90-day mortality rate after hepatic surgery compared to those without steatohepatitis (Vauthey et al., 2006). Meanwhile, oxaliplatin might cause sinusoidal dilatation or sinusoidal obstruction syndrome via generation of reactive oxygen species (ROS), or up-regulation of inflammation genes to induce hepatitis (McWhirter et al., 2013). Although the surviving patients have an association with improved liver function, the abnormal liver function induced by chemotherapy could interrupt and limit the treatment of patients with colon cancer (Sabbagh et al., 2015).

Traditional Chinese herbal medicine has been used to treat illnesses or symptoms of illness for thousands of years. Many studies of animal-liver injury models have proven that certain Chinese herbs or formulas, such as *Schisandra chinensis* (Wuweizi) (Hwang et al., 2013), curcumin (Girish and Pradhan, 2012), *Polygonum cuspidatum* (Zhang et al., 2012), *Gentiana asclepiadea* L. extracts (Mihailović et al., 2013), and *Rheum emodi* roots have protective effects for the liver (Akhtar et al., 2016). The Chinese herbal therapies demonstrated hepato-protective effectiveness via anti-inflammatory, antioxidant, anticancer, and immunomodulation effects (Wang et al., 2007). These defensive effects seem to reduce liver damage, even that resulting from chemotherapy. Furthermore, a recent cohort study demonstrated that the use of Chinese herbal medicine (CHM) may decrease the risk of death in patients with chronic hepatitis B receiving lamivudine treatment (Tsai et al., 2015).

In Taiwan, under the health insurance system, Western medicine combined with traditional Chinese medicine has been used to treat patients for many years, since CHM granules are supported by the National Health Insurance (NHI) system in Taiwan. The CHM is not only used to restore physical energy but also to reduce side effects resulting from radiotherapy and chemotherapy in patients suffering from cancer (Ye et al., 2015; Lin et al., 2013). These Chinese herbal products include single Chinese herbs and multi-herbal Chinese formulas. All of these CHM granules covered by the NHI program are manufactured by Good Manufacturing Practice (GMP)-certified pharmaceutical companies. The daily clinical practices of actual CHM granules usage are recorded in the NHI database. The purpose of the present study is to determine whether using CHM as an adjuvant therapy for the treatment of advanced colon cancer with chemotherapy has liver-protective effects, or contrarily, acts to increase the burden placed on the liver. Herein, we conducted a population-based retrospective cohort study of the NHI database to evaluate and compare the cumulative incidence of chronic hepatitis between CHM users and non-users in patients diagnosed with colon cancer.

2. Materials and methods

2.1. Data source

This study used reimbursement claim data from the Taiwan National Health Insurance Program. An NHI program was implemented in March 1995, which consists of 22.6 million individuals from a total population of 23.0 million in Taiwan, who were enrolled in this insurance program. The NHI is an obligatory universal health insurance program, offering comprehensive medical care coverage to 99% of the entire Taiwanese population and contracted with 97% of the hospitals and clinics (http://www.nhi.gov.tw/english/index.aspx). The National Health Insurance Research Database (NHIRD) covered every medical record, including use of traditional Chinese medicine treatment by the NHI. The datasets of the study consisted of registry for beneficiaries, ambulatory and inpatient care claims, and Registry for Catastrophic Illness from NHIRD. We used ambulatory and inpatient care records for cancer patients linked with the registry for Catastrophic Illness patients, within the period of 2000–2010, identify the study subjects for follow-up until the completion of the 2011 calendar year. Ambulatory care claims contain the International Classification of Disease, Ninth Revision, and Clinical Modification (ICD-9-CM) codes for one major and/or two secondary diagnoses, associated with individual's gender, date of birth and visit date. Inpatient care claims contain ICD-9-CM codes for one principal diagnosis and/or four secondary diagnoses. The Registry for Catastrophic Illness database contains data from those insured who suffer from major diseases and are granted exemption from co-payment. The registration with ICD-9-CM codes is also used for diagnosis by Chinese medical physicians, as requested by the NHI program. Because the NHIRD offers data to be used for the purpose of academic research, the present study was waived from informed consent. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115).

2.2. Study cohort identification

Colon cancer is one of the 31 categories of serious illnesses or injuries that result in a patient being issued with a Catastrophic Illness Certificate. The colon cancer cohort was comprised of patients who were newly diagnosed with colon cancer of ICD-9-CM code 153.x from 1997 to 2010 (n=74,028). We excluded patients of less than 18 years of age (n=43), and those who had withdrawn from insurance or were diagnosed with chronic hepatitis before the first diagnosis date of colon cancer (n=12,309). The 61,676 patients diagnosed with colon cancer from 1997 to 2010 years were included (Fig. 1). Chronic hepatitis patients coded by ICD-9-CM 571.4, associated with ICD-9-CM 153.x to indicate colon cancer, were identified. All eligible patients were followed up from the index date to December 31, 2011.

Those patients with colon cancer receiving acupuncture, and orthopedics and traumatology of TCM were excluded from this study. Participants using CHM for a period of more than 30 days with a diagnosis of colon cancer were defined as CHM users; whereas those without CHM outpatient records were defined as the non-CHM cohort group. The CHM user cohort index was further defined from the first

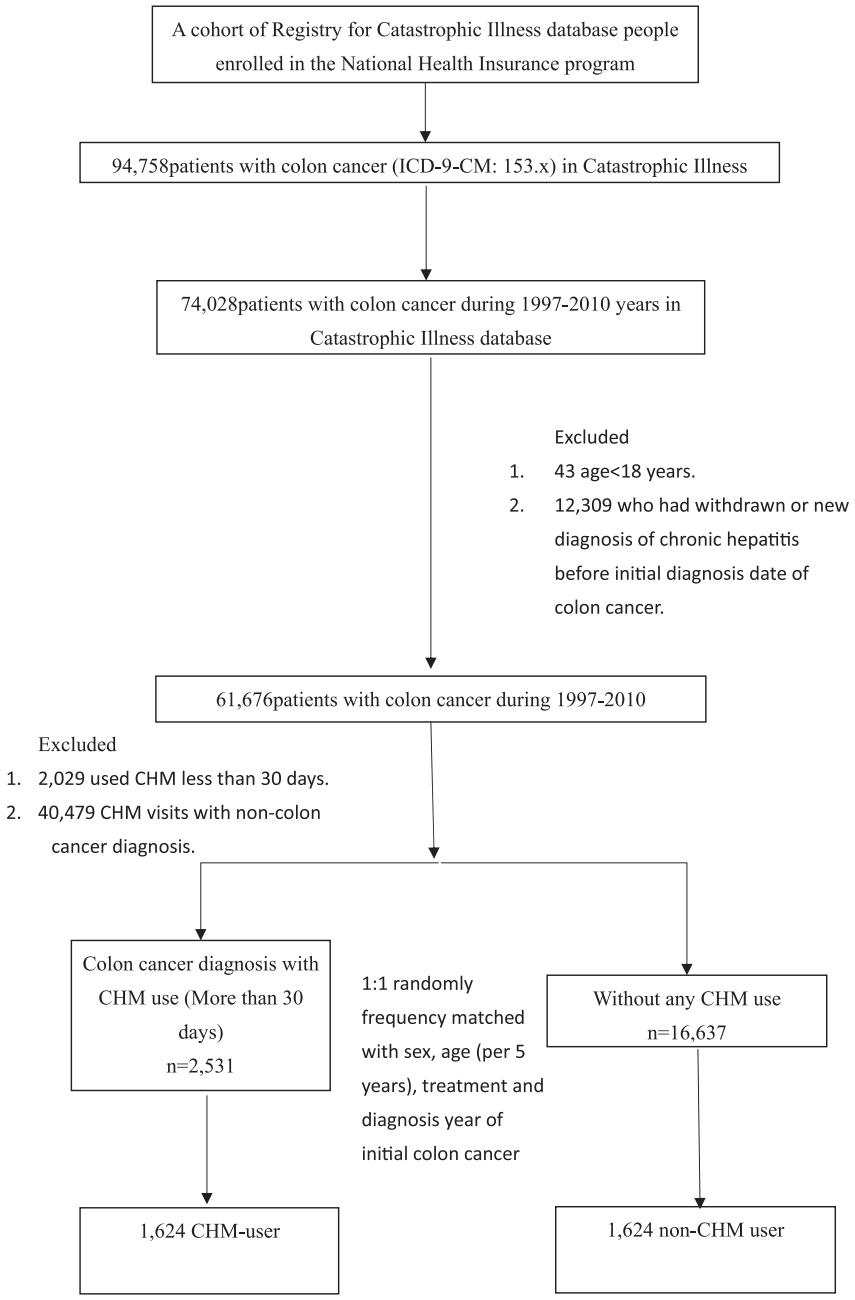

Fig. 1. Study population flowchart diagram. Of the total number of colon cancer patients registered in the NHIRD (n=94,758), 74,058 patients with colon cancer were diagnosed within the years 1997–2010. After excluding patients with missing information as well as matching 1:1 by age, CCI score, treatment and diagnosis of initial colon cancer, both groups contained 1,624 patients.

time of receiving CHM after initial diagnosis date of colon cancer.

We identified any potential confounders to chronic hepatitis, including the co-morbidities comprised of hypertension (ICD-9-CM: 401–405, A code: A260, A269), stroke (ICD-9-CM: 430–438, A290-A299), COPD (ICD-9-CM: 491, 492, 494, 496), asthma (ICD-9-CM: 493), diabetes (ICD-9-CM: 250, A code: A181), anemia (ICD-9-CM: 280–285), alcohol-related illness (ICD-9-CM: 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3) and cirrhosis (ICD-9-CM: 571, A code: A347). Furthermore, we characterized the treatment modalities, including surgery, chemotherapy and radiotherapy in the colon cancer patients, with or without association to chronic hepatitis. The resulting group included those patients with chronic hepatitis (ICD-9-CM: 571.4) whom had visited the clinic/hospital at least twice after the first colon cancer diagnosis date. Before matching, of the 61,676 patients with colon cancer, there were 745 patients diagnosed with chronic hepatitis during the period of 1997–2010.

2.3. Statistical analysis

Continuous variables were presented as mean and standard deviation; whereas categorical variables were described as number and percentage. Differences in proportions and means were estimated by chi-square test or t-test. A Cox proportional hazard model was used to estimate Hazard Ratio (HR) for CHM users compared to non-CHM users. For categorical covariates, Kaplan–Meier and log rank tests were performed to estimate the cumulative incidence of chronic hepatitis between CHM users and non-CHM users. A P value < 0.05 was considered statistical significance. SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analysis.

3. Results

3.1. Demographic characteristics

Of the 2531 CHM users and 16,637 non-CHM users among colon cancer patients identified between 1997 and 2010, with frequency matching of both groups for sex, age (per 5-year periods), treatment, index year and initial diagnosis year of colon cancer, there were 1624 patients included in each group. The mean of follow-up duration was 3.10 (median: 2.15) and 1.63 (median: 1) years for CHM and non-CHM cohorts, respectively. The demographic data, including age, gender, co-morbidities and treatment modalities between CHM users and non-CHM users with colon cancer patients, are shown in Table 1. The age, gender and treatment modalities of both cohorts had no statistical significance between CHM users and non-CHM users after matching. CHM users were linked with a higher proportion of COPD, asthma and cirrhosis as co-morbidities, in comparison with non-CHM users.

3.2. The cause-specific hazard ratio and 5-year cumulative incidence of chronic hepatitis

Univariate and multivariate Cox's proportional hazard model were estimated by the risk of chronic hepatitis hazard ratios (HRs) and 95% confidence interval (95% CI) in the cohort of CHM users vs. non-CHM users, during the period of 1997–2011, among colon cancer patients (Table 2). A total of 155 patients with chronic hepatitis were observed during the follow-up period. Kaplan-Meier analysis demonstrated that the cumulative incidence of chronic hepatitis were significantly lower in the CHM cohort compared to non-CHM cohort (log-rank test, $p < 0.0001$) (Fig. 2). With or without adjusted HR, CHM users had a lower risk of chronic hepatitis in comparison with non-CHM users. Those subjects over 60 years of age had a lower risk of chronic hepatitis than those in the 18–59 age group (HR: 0.58, 95% CI: 0.41–0.82). In general, cirrhosis was noted as a risk factor associated with chronic hepatitis in patients with colon cancer (HR: 2.26, 95% CI: 1.54–3.33), as shown in Table 2.

The incidence rates of chronic hepatitis between CHM users and non-CHM users were 14.29 and 31.25 per 1000 person-years, respectively, with statistical significance. Stratified by gender, the incidence rates of chronic hepatitis in both female and male CHM users were 14.91 and 13.81 per 1000 person-years, respectively. Both females (HR: 0.56, 95% CI: 0.35–0.91) and males (HR: 0.56, 95% CI: 0.36–0.87) in the CHM cohort group had a lower risk of developing chronic hepatitis than those in the non-CHM cohort group. We also observed that both subgroups of patients aged 18–59 and older than 60 in the CHM cohort had a lower risk of developing chronic hepatitis when compared with those in the non-CHM user cohort. Among those patients participating with and without co-morbidities, the patients with CHM use were less likely to have chronic hepatitis than those without CHM use. Of those colon cancer patients having undergone chemotherapy treatment, as well as those having undergone surgery without radiotherapy, the patients with CHM use had a significantly reduced incidence of chronic hepatitis compared to non-CHM users. Of note, those colon cancer patients treated with/without anti-cancer drugs, with CHM used as an adjuvant treatment, had a decreased risk of developing chronic hepatitis, with statistical significance, in comparison with the non-CHM users. The data, as shown in Table 3, indicates that CHM protects liver function in patients with colon cancer.

3.3. Single herbs and formulas associated with protection against chronic hepatitis

The 10 single herbs and multi-herbal CHM products (formulas) most commonly prescribed for patients with colon cancer are listed in Table 4. The composition of each formula was shown in supplementary Table 1. The average daily dose of each single herb and formula is from 0.8-4.3 g and 3.8–9.4 g, respectively. The prescription duration for each single herb and formula is from 12.6-15.4 days and 10.9–14.5 days, respectively. The effects of CHM use were further explored using a Cox proportional hazard regression analysis. The results demonstrate that eight single herbs and five formulas significantly decreased incidence of chronic hepatitis among colon cancer patients, as shown in Table 5.

Table 1
Characteristics of colon cancer patients according to the use of Chinese herbs and non-used.

Variable	Colon cancer patients				*p*-value
	Chinese herb medicine used				
	No (N =1624)		Yes (N =1624)		
	n	%	n	%	
Gender					0.99
Female	698	42.98	698	42.98	
Male	926	57.02	926	57.02	
Age group					0.99
18–59	663	40.83	663	40.83	
≥60	961	59.17	961	59.17	
Mean ± SD (years)[a]	62.64(11.81)		62.51(11.65)		0.5778
Comorbidity					
Hypertension	749	46.12	781	48.09	0.2606
Stroke	231	14.22	240	14.78	0.6538
COPD	224	13.79	323	19.89	< 0.0001
Asthma	122	7.51	173	10.65	0.0018
DM	332	20.44	342	21.06	0.6652
Anemia	319	19.64	342	21.06	0.3162
Alcohol-related illness	34	2.09	24	1.48	0.1852
Cirrhosis	159	9.79	249	15.33	< 0.0001
Treatment modality					0.99
No RT and no CT and no surgery for colon cancer	168	10.34	168	10.34	
Only radiotherapy	7	0.43	7	0.43	
Only chemotherapy	193	11.88	193	11.88	
Only colon cancer surgery	372	22.91	372	22.91	
RT+CT but no colon cancer surgery	48	2.96	48	2.96	
RT+colon cancer surgery but no CT	7	0.43	7	0.43	
CT+colon cancer surgery but no RT	682	42	682	42	
RT+CT+colon cancer surgery	147	9.05	147	9.05	
Follow time, year (mean, median)	1.63(1.00)		3.10(2.15)		
Interval between onset of colon cancer disease and the index date, days, median	215.5		188		0.3341

[a] Chi-Square test; *t*-test.

4. Discussion

The results of this study reveal that colon cancer patients associated with chemotherapy using CHM treatment had decreased incidence rates of chronic hepatitis compared to the non-CHM group. These results remained consistent after adjustment for age, sex, and with or without co-morbidities. The cumulative incidence rates of chronic hepatitis in patients with colon cancer remained lower in CHM users in comparison with non-CHM users for a follow-up period of up to 5 years. The data suggests that using CHM as an adjuvant therapy not only does not increase the burden on the liver but, on the contrary, has a protective effect on the liver. One particular data point of interest was that those patients over sixty years of age had a lower risk of chronic hepatitis compared to the patients aged between 18 and 59 years. This

Table 2
Cox model with hazard ratios and 95% confidence intervals of chronic hepatitis (associated with or without Chinese herbal medicine used) and covariates among colon cancer patients.

Variable	No. of event (n=155)	Crude[a]			Adjusted[b]		
		HR	(95%CI)	p-value	HR	(95%CI)	p-value
Chinese herb medicine used							
No	83	1.00	reference		1.00	reference	
Yes	72	0.56	(0.41–0.78)	0.0005	0.53	(0.38–0.74)	0.0001
Gender							
Female	69	1.00	reference		1.00	reference	
Male	86	0.92	(0.67–1.27)	0.6276	0.9	(0.65–1.25)	0.5293
Age group							
18–59	81	1.00	reference		1.00	reference	
≥60	74	0.64	(0.46–0.87)	0.0048	0.58	(0.41–0.82)	0.0022
Comorbidity							
Hypertension	77	1.12	(0.82–1.54)	0.4637	1.29	(0.91–1.82)	0.1547
Stroke	21	0.98	(0.62–1.56)	0.9413	1.13	(0.69–1.86)	0.6238
COPD	20	0.74	(0.46–1.18)	0.2072	0.87	(0.52–1.46)	0.6065
Asthma	10	0.71	(0.38–1.35)	0.2989	0.75	(0.38–1.49)	0.4126
DM	33	1.05	(0.71–1.54)	0.8113	0.94	(0.63–1.41)	0.7793
Anemia	26	0.80	(0.53–1.22)	0.3014	0.77	(0.5–1.19)	0.2397
Alcohol-related illness	3	1.26	(0.4–3.95)	0.6942	0.84	(0.26–2.7)	0.7704
Cirrhosis	38	2.06	(1.42–2.97)	0.0001	2.26	(1.54–3.33)	< 0.0001

[a] Crude HR represented relative hazard ratio.
[b] Adjusted HR represented adjusted hazard ratio: mutually adjusted for Chinese herbal medicine used, sex, age, co-morbidity, treatment and drugs used in Cox proportional hazard regression.

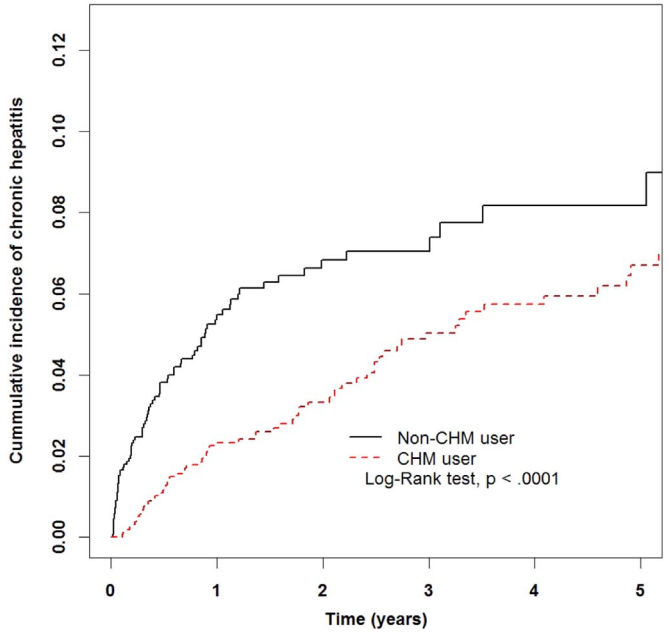

Fig. 2. The estimated cumulative incidence of chronic hepatitis between those treated or not treated with CHM in patients with colon cancer cohort by Kaplan–Meier analysis.

could be attributed to the more elderly patients having been prescribed different drug selections, or lower doses during chemotherapy treatment to prevent severe side effects. A retrospective cohort study, which identified 6,262 patients aged 65 years and older with resected stage III colon cancer, demonstrated that the strongest determinant for chemotherapy was age at diagnosis (Schrag et al., 2001). Our results demonstrated that patients with cirrhosis had a higher risk of co-morbidity compared to the patients without cirrhosis in CHM users. This could be due to cirrhosis creating more major postoperative complications, and thus a higher mortality rate in patients with colon cancer (Sabbagh et al., 2016). However, due to the lack of biological data and image identification, it was not possible to distinguish the severity of the diseases in those patients with liver cirrhosis or chronic hepatitis in the colon cancer cohort. With regard to treatment modalities, only those colon cancer patients receiving chemotherapy and surgery without radiotherapy showed a significant reduction in incidence of chronic hepatitis. Moreover, CHM use among patients with/without anticancer drug combinations demonstrated a significantly lower incidence rate of chronic hepatitis compared with non-CHM users. These results further imply that CHM indeed had a protective effect on liver function.

The study also revealed that distribution of co-morbidities between the non-CHM user group and CHM user group showed differences. The occurrence rates of certain diseases, such as COPD, asthma, and cirrhosis were more significant in the CHM group ($P < 0.05$). It is important to note that in Taiwan, patients with COPD and asthma were accustomed to using traditional Chinese medicine to prevent recurrence and improve health (Cheng et al., 2015). Also of note, liver cirrhosis in patients most commonly developed due to viral hepatitis rather than alcohol-related hepatitis, or resulting from a fatty liver (Lin and Kao, 2015; Ott et al., 2012). It has been demonstrated in a previous study that those Taiwanese patients with liver diseases often took traditional Chinese medicine for further management (Hsueh et al., 2015). Thus, due to these differing treatment behaviors among Taiwanese patients, more case numbers with COPD, asthma and cirrhosis were included in the CHM group.

One of the characteristics of traditional Chinese medicine is the system referred to as "syndrome differentiation and treatment", which is used in order to make a definitive TCM diagnosis. This diagnosis is arrived at by determining a "pattern", through analysis of tongue features and pulse performance, which is ultimately used to provide suitable treatment. By virtue of this, patients suffering from the same disease, but demonstrating different symptoms, such as differing tongue and pulse diagnoses, would be treated with the use of different herbal drugs. The Chinese herbal drugs used in patients with colon cancer are shown in Table 4.

This study reveals that the ten most commonly used single herbal medicines were *Hedyoti sdiffusa, Sculellaria barbatae, Astragalus membranaceus, Atractylodes macrocephala, Salvia miltiorrhiza, Millettia dielsiana, Magnolia officinalis, Rheum rhabarbarum, Zizyphi spinosi Semen,* and *Scutellaria baicalensis*. These drugs had the effects of clearing the heat and dampness, invigorating qi and strengthening the spleen, promoting blood circulation, regulating the stomach to reduce adverse qi, relieving mental stress, and helping with sleep deprivation. Furthermore, the ten most commonly used CHM formulas were Xiang Sha Liu Jun Zi Tang, Jia Wei Xiao Yao San, Bu Zhong Yi Qi Tang, Shen Lin Bai Zhu San, Ping Wei San, Ma Zi Ren

Table 3
Incidence rates, hazard ratio and confidence intervals of chronic hepatitis for colon cancer patients with and without use of Chinese herbalmedicine, stratified for sex, age, co-morbidity and treatment.

Variables	Chinese herb used						Crude HR	Adjusted HR
	No (N=1624)			Yes (N=1624)				
	Event	Person years	IR[a]	Event	Person years	IR[a]	(95%CI)	(95%CI)
Total	83	2647	31.35	72	5038	14.29	0.56(0.41–0.78)***	0.53(0.38–0.74)***
Gender								
Female	36	1085	33.19	33	2213	14.91	0.57(0.35–0.92)*	0.56(0.35–0.91)*
Male	47	1563	30.07	39	2825	13.81	0.55(0.36–0.85)**	0.56(0.36–0.87)**
Age								
18–59	46	1114	41.29	35	2022	17.31	0.52(0.34–0.82)**	0.51(0.33–0.80)**
≥60	37	1533	24.13	37	3015	12.27	0.62(0.39–0.99)*	0.60(0.37–0.96)*
Comorbidity								
No	29	943	30.75	12	1428	8.40	0.34(0.17–0.68)**	0.32(0.16–0.65)**
Yes	54	1704	31.68	60	3609	16.62	0.65(0.45–0.94)*	0.66(0.45–0.96)*
Treatment								
No RT and no CT and no surgery for colon cancer	9	203	44.28	11	493	22.31	0.62(0.25–1.51)	0.60(0.23–1.52)
Only radiotherapy	0	3	0.00	0	13	0.00	–	–
Only chemotherapy	10	165	60.74	8	429	18.63	0.4(0.15–1.06)	0.44(0.16–1.17)
Only colon cancer surgery	16	749	21.38	17	1328	12.80	0.66(0.33–1.33)	0.62(0.31–1.25)
RT+CT but no colon cancer surgery	1	69	14.42	0	133	0.00	–	–
RT+colon cancer surgery but no CT	0	16	0.00	0	30	0.00	–	–
CT+colon cancer surgery but no RT	44	1206	36.48	31	2153	14.40	0.52(0.33–0.83)**	0.51(0.32–0.82)**
RT+CT+colon cancer surgery	3	236	12.71	5	459	10.88	1.15(0.27–4.89)	1.17(0.27–5.10)
Anti-cancer drugs used								
No	29	1027	28.24	28	1980	14.14	0.58(0.34–0.99)*	0.55(0.32–0.94)*
Yes	54	1620	33.32	44	3058	14.39	0.56(0.37–0.84)**	0.54(0.36–0.80)**

Abbreviation: IR, incidence rates, per 1000 person-years; HR, hazard ratio; CI, confidence interval.

[a] Adjusted HR represented adjusted hazard ratio: mutually adjusted for Chinese herbal medicine used, sex, age, co-morbidity, treatment and drug used in Cox proportional hazard regression.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 4
Ten most commonly prescribed herbal formulas.

Herbal formula	Frequency	Number of person-days	CHM sum of dose (g)	Average daily dose (g)	Average duration for prescription (days)
Single herb					
Hedyotisdiffusa	5339	78122	232553.5	3	14.6
Scutellariabarbata	4325	63932	209385.4	3.3	14.8
Astragalusmembranaceus	2288	28740	47959.1	1.7	12.6
Atractylodesmacrocephala	2030	26884	74832	2.8	13.2
Salvia miltiorrhiza	1939	26507	37934.8	1.4	13.7
Millettiadielsiana	1872	26173	37438.6	1.4	14
Magnolia officinalis	1954	23244	34248.7	1.5	11.9
Rheum rhabarbarum	1793	22779	19107.4	0.8	12.7
ZizyphiSpinosi Semen	1362	20994	55315.8	2.6	15.4
Scutellariabaicalensis	1530	19815	84727.1	4.3	13
Formula					
Xiang Sha Liu Jun Zi Tang	3201	41442	208004.1	5	12.9
Jiawei Xiaoyao San	1867	27049	227945.6	8.4	14.5
BuzhongYiqi Tang	2084	25895	191926.1	7.4	12.4
Shen Lin Bai Zhu San	1789	23715	186290.2	7.9	13.3
Ping Wei San	1621	19565	142386.1	7.3	12.1
Ma Zi Ren Wan	1334	18419	70174.9	3.8	13.8
Gui Pi Tang	1240	16881	87114.5	5.2	13.6
Sheng Mai Yin	1157	15096	62688.6	4.2	13
Ban Xia Xie Xin Tang	1345	14726	138562.3	9.4	10.9
Gan Ru Yin	1254	14629	62144.1	4.2	11.7

Table 5
Hazard Ratios and 95% confidence intervals of chronic hepatitis risk associated with Chinese herbal medicine use inpatients with colon cancer.

CHM prescription	Chronic hepatitis		Hazard ratio (95% CI)	
	n	No. of Event	Crude[a]	Adjusted[b]
Non-CHM users	83	1624	1(reference)	1(reference)
CHM users				
Single herb				
Hedyotisdiffusa	452	17	0.51(0.30–0.86)*	0.50(0.29–0.85)*
sculellariabarbata	401	19	0.64(0.39–1.06)	0.63(0.38–1.05)
Astragalusmembranaceus	329	15	0.58(0.33–1.01)	0.60(0.34–1.05)
Atractylodesmacrocephala	359	12	0.44(0.24–0.81)**	0.42(0.23–0.79)**
Salvia miltiorrhiza	304	10	0.41(0.21–0.80)**	0.36(0.19–0.71)**
Millettiadielsiana	286	9	0.41(0.20–0.82)*	0.36(0.18–0.72)**
Magnolia officinalis	311	9	0.38(0.19–0.75)**	0.35(0.17–0.71)**
Rheum rhabarbarum	248	3	0.17(0.05–0.53)**	0.15(0.05–0.49)**
ZizyphiSpinosi Semen	245	9	0.48(0.24–0.95)*	0.38(0.19–0.77)**
Scutellariabaicalensis	307	10	0.44(0.23–0.85)*	0.38(0.19–0.74)**
Formula				
Xiang Sha Liu Jun Zi Tang	426	17	0.54(0.32–0.91)*	0.56(0.33–0.96)*
Jiawei Xiaoyao San	284	17	0.74(0.44–1.26)	0.66(0.38–1.13)
BuzhongYiqi Tang	304	14	0.58(0.33–1.03)	0.58(0.33–1.03)
Shen Lin Bai Zhu San	277	13	0.57(0.32–1.04)	0.55(0.30–1.02)
Ping Wei San	241	7	0.37(0.17–0.80)*	0.35(0.16–0.77)**
Ma Zi Ren Wan	152	2	0.17(0.04–0.68)*	0.16(0.04–0.65)*
Gui Pi Tang	241	7	0.38(0.17–0.81)*	0.34(0.16–0.76)**
Sheng Mai Yin	166	5	0.37(0.15–0.92)*	0.36(0.15*–0.91)*
Ban Xia Xie Xin Tang	258	11	0.57(0.30–1.07)	0.53(0.28–1.02)
Gan Ru Yin	218	16	0.93(0.54–1.59)	0.90(0.52–1.57)

***p < 0.001.
[a] Crude HR represented relative hazard ratio.
[b] Adjusted HR represented adjusted hazard ratio: mutually adjusted for Chinese herb medicine used, sex, age, co-morbidity, treatment and drug used in Cox proportional hazard regression.
* p < 0.05,
** p < 0.01,

Wan, Gui Pi Tang, Sheng Mai Yin, Ban Xia Xie Xin Tang, and Gan Ru Yin. The results of this study shared similarities with another cross-sectional study of newly diagnosed colon cancer patients who received surgery, and used CHM, between 2004 and 2008 (Chao et al., 2014). They had the effects of strengthening qi, nourishing the blood, and of dispersing and rectifying the depressed liver qi, in accordance with TCM theory. These formulas contributed to decreased side effects induced by chemotherapy, such as bone marrow suppression and gastrointestinal upset. Certain drugs, as shown in Table 5, significantly reduced incidence of chronic hepatitis in patients with colon cancer, with the exception of *Scutellaria barbatae* and *Astragalus membranaceus*. The data demonstrates that these drugs were essentially harmless to the liver, and may effectively protect the liver from injury due to chemotherapy.

The single herbs used in CHM each offer unique effects for patients, and are thus employed for the treatment for specific symptoms. In regards to the characteristics of specific single herbs, and the mechanisms operating therein, *Hedyotis diffusa* is commonly used for cancer treatment and also useful in treating hepatitis with a heat and dampness pattern. It has been hypothesized that these anti-cancer mechanisms might be associated with mitochondrion-mediated apoptosis (Lin et al., 2010), suppression of the signal transducer and activator of the transcription 3 (STAT3) pathway (Cai et al., 2012), or inhibiting tumor angiogenesis (Lin et al., 2011, 2013). Its hepato-protective effects were via promotion of antioxidants and the subsequent scavenging of free-radicals (Gao et al., 2015; Kagoo and Darling, 2014). *Atractylodes macrocephala* had the effect of strengthening the spleen and clearing dampness, and is commonly used to treat diarrhea. A study utilizing rat models demonstrated that the *Atractylodes macrocephala* polysaccharide had therapeutic and protective effects against hepatic ischemia-reperfusion injury, which might be associated with its antioxidant properties, inhibiting lipid peroxidation and inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Jin et al., 2011). *Salvia miltiorrhiza* and *Millettia dielsiana* are most commonly used to promote blood circulation and remove blood stasis. Many studies have suggested that *Salvia miltiorrhiza* could protect the liver from injury via anti-fibrotic, anti-oxidative, anti-inflammatory and anti-apoptotic effects (Duval et al., 2014). Compared to 5-FU alone, co-treatment with Tanshinone IIA, as extracted from *Salvia miltiorrhiza*, caused a reduction in tumor volumes and decreased P-glycoprotein (*p*-gp) and microtubule-associated protein light chain 3 (LC3)-II expression in rat models (Su, 2012). *Millettia dielsiana* was found to have potent anti-inflammatory effects via decreasing NO production and inhibiting TNF-α secretion (Ye et al., 2014). *Magnolia officinalis* was used to eliminate flatulence. In recent years, studies of *Magnolia officinalis* have revealed a substantial increase in the variety of therapeutic roles it plays in the body. In addition to the anti-cancer effect, liver protection was through protecting against oxidative stress-related toxicity (Ponnurangam et al., 2012; Rajgopal et al., 2015). It has also been considered to have potential therapeutic effectiveness in treating alcohol-related liver disease (Lu et al., 2012). In a cholestatic hepatitis rat model study, emodin, an anthraquinone derivative from *Rheum rhabarbarum*, was found to have a protective effect on hepatocytes and a restorative effect on cholestatic hepatitis due to its anti-inflammatory qualities (Ding et al., 2008). Rhubarb extract has been noted to possibly decrease hepatic triglyceride content and down-regulation of pro-inflammatory markers, such as TNF-α, IL-6, MCP-1 and COX-2 in the liver of mice (Neyrinck et al., 2014). The components extracted from *Scutellariae radix* and *Rheum rhabarbarum* were found to effectively prevent hepatic fibrosis, mainly via down-regulation of antioxidant enzymes, decreasing oxidative stress and cytoskeleton dysregulation (Pan et al., 2015). *Zizyphi spinosi* semen was used to treat sleep disorders or insomnia, which are common in cancer patients (Ancoli-Israel, 2015). A post-hoc questionnaire analysis revealed that sleep problems were asso-

ciated with an increased risk of earlier death, cancer progression and poor treatment response in chemo-naïve patients with metastatic colorectal cancer (Innominato et al., 2015). The mechanism of *Zizyphi spinosi* semen in helping with sleep disorders may be associated with the GABA system and 5-HT 1A receptors (Shi et al., 2014). Although few studies have mentioned the protective effects of *Zizyphi spinosi* semen on the liver, there have also been no obvious adverse effects reported (Xie et al., 2013). In our study, *Zizyphi spinosi* semen is considered to be a protector of liver function, while more studies are needed to validate and further identify the mechanisms of liver protection. The role of *Scutellaria baicalensis* in liver protection has been the focus of several studies. Baicalin, a flavonoid isolated from *Scutellaria baicalensis*, has displayed hepato-protective effects in alcohol-induced liver injury through inhibiting oxidative stress, decreasing inflammatory response, and modulating the activation of the Sonic Hedgehog pathway (Wang et al., 2016). Recently, baicalein was demonstrated to inhibit cisplatin-induced hepatic oxidative stress and inflammation in mice through decreasing superoxide dismutase, catalase, glutathione peroxidase, glutathione-S transferase and glutathione reductase, and suppression of TNFα and IL-6 induction (Niu et al., 2016). Through the analysis of the ten most common single herbs used to treat Taiwanese patients with colon cancer, our study provides valuable evidence to provide further insight into the effects of CHM on protecting the liver from various forms of chemotherapeutic drug-induced injury. Altogether, the extracted ingredients, biological activities and their experimental models of eight significant single herbs were summarized in the supplementary Table 2.

As well as single herbs, Chinese herbal medicine also adopts herbal formulas, which possess a variety of potential benefits for patients. It is worth noting that of the most commonly prescribed TCM formulas, Xiang Sha Liu Jun Zi Tang and Gui Pi Tang act to strengthen the spleen's qi, thus assisting the gastrointestinal tracts to absorb nutrients. In comparison, Ping Wei San and Ma Zi Ren Wang are used to empty the stomach, promote gastrointestinal motility, clear the hollow viscera and relieve intestinal stasis. These formulas, however, seem to also possess a protective effect for the liver through gastrointestinal modulation.

Needless to say, these herbal compounds are in actual fact composed of single herbs, the qualities of which are mentioned above. For instance, Xiang Sha Liu Jun Zi Tang and Gui Pi Tang contain *Atractylodes macrocephala*, Ping Wei San contains *Magnolia officinalis*, and Ma Zi Ren Wang contains *Magnolia officinalis* and *Rheum rhabarbarum*. According to TCM theory, the two former formulas "diminish where there is superabundance, and supplement where there is deficiency". These dual functions operate with the goal of improving the health of the body. In fact, chemotherapy is particularly noted to induce severe diarrhea, especially irinotecan, and such a condition serves to limit the treatment effectiveness (Chowbay et al., 2003). Furthermore, there appears to be no effective or definitive way to deal with such a therapeutic challenge (Kee et al., 2015; Swami et al., 2013). As such, Xiang Sha Liu Jun Zi Tang and Gui Pi Tang could be reasonable options in treating the diarrhea induced by chemotherapy. Chemotherapy-induced constipation has been noted as another common issue suffered by patients (McQuade et al., 2016). To this end, Ping Wei San and Ma Zi Ren Wang could be taken into consideration to solve constipation effectively and simultaneously further protect liver function. Sheng-Mai-Yin (SMY) is widely used to prevent excessive sweating and fatigue. *Panax ginseng* and *Schizandrae fructus*, two major components in SMY, have been reported to be effective in treating the symptom of fatigue, commonly suffered by patients undergoing chemotherapy, but also offer protective effects in treating viral hepatitis and chemical-induced hepatic injury, respectively (Wang et al., 2010).

In general, cancer patients have a variety of alternative treatment options to complement and be used in conjunction with western medicine; most of these medications are metabolized through the liver and excreted via the kidneys. However, the issues surrounding possible complications arising from drug interactions between Chinese and western medicines are unclear, and deserve closer observation and analysis. The present study obtained data from the NHIRD, a government-run, single-payer NHI program that covers over 99% of the Taiwanese population and 93% of healthcare institutes, which ensures this study represents the general population with minimal selection bias and offers comprehensive results of both CHM and non-CHM users among colon cancer patients. Noted limitations of our study include the fact that we did not have each patient's performance status, lacked specific chemotherapy dose and method, data concerning use of additional alternative medicine, laboratory data (transaminase, bilirubin, alkaline phosphatase, Gamma-glutamyl transferase, serum albumin, etc...), and lifestyle details, which were not collected in the NHI database. Due to these data limitations, we did not have access to patients' exact clinical conditions and biochemical data to evaluate the severity of hepatitis within the two studied cohort groups.

5. Conclusions

This nationwide retrospective cohort study provides information to further the notion that CHM, when used as an adjuvant modality, may have a significant impact on liver protection in patients with colon cancer. This study also suggests that CHM may reasonably be used as an integral element of effective therapy to prevent subsequent incidence of chronic hepatitis in colon cancer patients associated with chemotherapy. Further research is still needed to investigate specific interactions and mechanisms at play when CHM is used as an adjuvant therapy with western medical treatments.

Authors' contributions and conflicts

THL wrote the manuscript and interpreted the data. HRY provided study materials. JHC collected, assembled and analyzed the data. STH designed, conceived the study and wrote the manuscript. KCH, HRY, JHC, MFS, HHC, and STH approved the final manuscript. The authors declare that there are no conflicts of interest.

Acknowledgements

This study was supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212–133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 105–2325-B-039-003), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. This work was also supported and funded by Ministry of Science and Technology with MOST 105–2320-B-039-035 and China Medical University Hospital with DMR-106-005. The authors would like to thank James Waddell, who is a Canadian, for the critical reading and revision of our manuscript.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jep.2017.03.027.

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