Journal of Food and Nutrition Research, 2016, Vol. 4, No. 2, 108-114
Available online at http://pubs.sciepub.com/jfnr/4/2/7

DOI:10.12691/jfnr-4-2-7

Chinese Herbal Medicine Safflower (*Flos carthami*) Does Not Increase Bleeding Complications: A Population-based Cohort Study

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Abstract Safflower (*Flos carthami*; FC) has been used widely as a food additive, as a coloring and flavoring agent. It has also been used as a Chinese herbal medicine for improving blood flow and resolving thrombosis. This study investigated whether the risk of bleeding complications is increased among FC users. We conducted a retrospective study involving a test group that used FC and a control (non-FC users) group. The participants were aged 18 years and above, and were recruited from the 2000 – 2006. The participants were from beneficiaries of LHID2000. The FC cohort included participants who had been prescribed FC accumulated for more than 30 days, whereas the non-FC cohort included people who were not using FC prescriptions. The compared cohort individuals were randomly selected at a ratio of 1:4 and frequency matched by age, gender, and index year from FC user cohort group. The primary outcome was a new diagnosis of bleeding disorders including gastrointestinal (GI) bleeding (ICD-9-CM: 578.0, 578.1, 578.9), intracranial hemorrhage (ICD-9-CM: 432.0, 432.9), and blood transfusions (ICD-9-CM op-code: 99.0). The results showed that the proportions of participants with bleeding disorders were 2.6% and 2.3% in the FC and non-FC cohorts, respectively (P = 0.6675). In univariate and multivariate Cox's proportional hazard regression models, the adjusted hazard ratio for bleeding disorders was 0.86 for the FC cohort relative to the non-FC cohort (P = 0.6094). In conclusion, the risk of bleeding complications was not increased among Chinese herbal medicine FC users.

Keywords: *bleeding disorder, chinese herbal medicine, safflower (Flos carthami), national health insurance database, population-based cohort study*

Cite This Article: Lih-Hwa Lin, Jen-Huai Chiang, Pei- Chi Chou, Po-Chi Liao, San-Yuan Wu, Kao-Sung Tsai, Huey-Yi Chen, Yung-Hsiang Chen, and Wen-Chi Chen, "Chinese Herbal Medicine Safflower (*Flos carthami*) Does Not Increase Bleeding Complications: A Population-based Cohort Study." *Journal of Food and Nutrition Research*, vol. 4, no. 2 (2016): 108-114. doi: 10.12691/jfnr-4-2-7.

1. Introduction

The use of *Flos carthami* (FC) (the flowers of *Carthamus tinctorius* L.) as a coloring and flavoring agent has increased as a food additive. It is also named Hong Hua in Chinese and it has been applied widely to relieve pain, improve blood circulation, remove blood stasis (thrombus), and promote blood regeneration in traditional Chinese medicine (TCM) for centuries [1,2,3]. FC is an essential component of a number of classic herbal formulas (traditional Chinese compound preparations) for eliminating thrombosis and rectifying blood flow, and the common decoctions include Bu Yang Huan Wu Tang, Tao Hong Si Wu Tang, Xue Fu Zhu Tang, Shen Tong Zhu Yu Tang, Fu Yuan Huo Xue Tang and Tong Qiao Huo Xue Tang [4,5,6,7].

The safflor yellow (A) (chemical identity: 6-β-D-Glucopyranosyl-2, 3, 4, 4a, 6, 9b-hexahydro-3, 4, 6, 7-tetrahydroxy-2-(hydroxymethyl)-8-[3-(4-hydroxyphenyl)-1-oxo-2-propenyl]-9H-pyrano[3, 2-b]benzofuran-9-one) is one of the flavonoids in FC, and its pharmacological actions are lowering blood pressure, protecting cardiac muscle, and suppressing immune function [8,9]. Many studies also indicated that FC can promote blood flow, reduce blood viscosity, decrease the formation of blood clots, remove thrombus, thus, prevent cardiovascular diseases [10,11].

FC is composed of some trace elements that play an important role in the production and storage of insulin. The element is involved in hundreds of enzymatic functions in the body, and it regulates blood pressure and removes thrombus. Moreover, FC could be a potential alternative adjuvant antitumor medicine for several specific malignant tumors and a modality for overcoming multidrug resistance in cancers [12], and it has been determined to potentially exert antilithic effects against nephrolithiasis and urolithiasis *in vitro* and in animal models [11,13,14,15].

Although FC can improve blood circulation and promote blood vessel relaxation, it is uncertain whether FC increases the risk of bleeding complications. Gastrointestinal (GI) bleeding and intracranial hemorrhage are common bleeding disorders. Drugs associated with GI bleeding include anticoagulants (heparin, warfarin), nonsteroidal anti-inflammatory drugs (e.g., aspirin), clopidogrel, and selective serotonin reuptake inhibitors. GI bleeding is a highly prevalent and potentially fatal disorder that causes a significant economic burden worldwide [16-23]. Prior studies indicated that patients taking warfarin have a higher risk of intracranial hemorrhage upon head trauma in the United States [24,25,26,27], and patients taking anticoagulants before head trauma have a higher risk of intracranial hemorrhage and a higher mortality rate [28,29,30,31,32]. Thus, in the present study, we investigated whether FC increases the risk of bleeding disorders, especially when used in combination with anticoagulants.

2. Materials and Methods

2.1. Database

The National Health Insurance Administration, Ministry of Health and Welfare in Taiwan, launched a single-payer program of National Health Insurance (NHI) since 1995, and all residents are compulsorily to join this program. The coverage rate has already approached 99% of 22.9 million residents since 1997, and 97% of hospitals and 92% of clinic have contracted with NHI [33,34,35]. The National Health Insurance Research Database (NHIRD) is supervised by the National Health Research Institutes in Taiwan, and Longitudinal Health Insurance Database 2000 (LHID2000). The dataset containing all medical expenses, diagnosis, and claims of patients between 1996-2012. These data was randomly sampled from those beneficiaries of the NHID between 1996 and 2000 and all the original claim data of one million individuals were included.

Personal information was scrambled to protect privacy, thus, the database is authorized for research and medical purpose in Taiwan. Approval from institutional review board of China Medical University Hospital was obtained the number of CMUH104-REC2-115. Since the identification number of each patient had already been encrypted for privacy protection, and the informed consent was then waived.

2.2. Study Design and Subjects

The retrospective cohort study was retrieved with two cohorts (FC and non-FC users with aged 18 years and above) from the 2000 - 2006 beneficiaries of LHID2000. The final date of follow-up was Dec. 31, 2011 and the duration was at least 5 years. There were variables of prescription drug use for both TCM and western medicine in LHID2000, including drug name, drug dose, and duration of drug use. FC cohort was the patient with prescriptions of FC accumulated for more than 30 days, whereas non-FC cohort was the patient without prescription of FC who was randomly selected in a ratio of 1:4 and matched by age (within 5 years), gender, and index year (for the statistical efficiency, 1:4 matching is to increase the power and to control possible confounding). The index year was defined as the year of taking FC in the FC cohort, and was randomly assigned from 2000 - 2006 years corresponding to index years of FC cohort in non-FC cohort. Subjects who have the history of bleeding disorders and major trauma before the index date were excluded from this study. Therefore, this study population will represent patients with aged 18 years and above. Then International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) was used to describe diagnoses.

2.3. Outcome

The primary outcome was measured at the time point that the patient newly diagnosed as bleeding disorders including GI bleeding (ICD-9-CM: 578.0, 578.1, 578.9), intracranial hemorrhage (ICD-9-CM: 432.0, 432.9) and blood transfusions (ICD-9-CM op-code: 99.0). Bleeding disorders were confirmed and stop tracked if GI bleeding disorders and intracranial hemorrhage were diagnosed at outpatient departments at least 3 times or inpatient claims once, and blood transfusion procedure was administered once. Subjects with no hemorrhagic disease were traced to the end of the study. Both cohorts were followed until December 31, 2011 or occurrence of bleeding disorder.

2.4. Potential Confounders

In this study, the comorbidities were considered as potential confounders as follows, hypertension (ICD-9-CM: 401-405, A code: A260, A269), heart disease (ICD-9-CM: 410-429), hyperlipidemia (ICD-9-CM: 272.3, 272.4), urinary stone (ICD-9-CM: 592, 594.1), peptic ulcer (ICD-9-CM: 533, A code: A341), cancer (ICD-9-CM: 140-239) and anemia (ICD-9-CM: 280-285). Anticoagulant users were patients having taken anticoagulant medications, including aspirin, clopidogrel, dipyridamole, ticlopidine and warfarin, for more than 30 days during the follow-up period.

2.5. Statistical Analyses

Means and standard deviations were described for continuous variables and percentages were described for categorical variables. Comparing two groups were performed by using Student's *t*-test for continuous variables and Pearson's Chi-squared test for categorical variables. Cox proportional hazard regression models were used to estimate the effect of FC on survival analysis determined by adjusted hazard ratio (HR) with 95% confidence interval (CI). All analyses were carried out with SAS statistical software (version 9.4 for Windows; SAS Institute, Inc., Cary, NC, USA). All statistical tests

were determined at significant level of 0.05 in two-tailed tests.

3. Results

The study population consisted of 577 people who were taking FC (FC cohort) and 2308 people who were not taking FC (non-FC cohort). The participants were matched at a ratio of 1:4 for gender, age, and index year. For both cohorts, the proportions of females and males were 62.74% and 37.26%, respectively. The conditional relative frequencies of 18–39, 40–64, and ≥65 years age groups were 50.43%, 39.51%, and 10.05%, respectively in both cohorts. The mean participant age was 42.39 years for the FC cohort and 42.33 years for the non-FC cohort, which were not statistically significant (P = 0.9309) (Table 1).

Table 1. Demographic characteristics of the study population

Variables	Non-*Flos carthami* (n=2308)		*Flos carthami* (n=577)		*P* value
	n	%	n	%	
Gender					
Female	1448	62.74	362	62.74	0.99[1]
Male	860	37.26	215	37.26	
Age, years					
Mean (SD)	42.33 (15.06)		42.39 (15.08)		0.9309[2]
Age group					
18-39 years	1164	50.43	291	50.43	0.99[1]
40-64 years	912	39.51	228	39.51	
≥ 65 years	232	10.05	58	10.05	

[1]Chi-squared test and [2]Student's *t*-test comparing subjects between with and without *Flos carthami* group.

The proportions of participants with bleeding disorders were 2.6% for FC users and 2.3% for non-FC users, with no statistically significant difference between the two cohorts (P = 0.6675). The proportions of participants taking anticoagulants were 11.09% and 5.5% for the FC and non-FC cohorts, respectively (P < 0.0001). Moreover, the risks of comorbidities were higher in the FC cohort than in the non-FC cohort as follows: hypertension, 17.68% vs. 9.71% (P < 0.0001); heart disease, 10.05% vs. 3.64% (P < 0.0001); hyperlipidemia, 5.20% vs. 2.47% (P = 0.0006); urinary stones, 3.47% vs. 1.47% (P = 0.0016); and peptic ulcer, 5.55% vs. 3.38% (P = 0.0151) (Table 2).

Table 2. The percentage of bleeding disorders, using anticoagulants and comorbidity for study population

Variables	Non-*Flos carthami* (n=2308)		*Flos carthami* (n=577)		*P* value
	n	%	n	%	
Bleeding disorders	53	2.30	15	2.60	0.6675
Taking anticoagulants[1]	127	5.50	64	11.09	<.0001***
Comorbidity					
Hypertension[2]	224	9.71	102	17.68	<.0001***
Heart disease[3]	84	3.64	58	10.05	<.0001***
Hyperlipidemia[4]	57	2.47	30	5.20	0.0006***
Urinary stones[5]	34	1.47	20	3.47	0.0016**
Peptic ulcer[6]	78	3.38	32	5.55	0.0151*
Anemia[7]	43	1.86	17	2.95	0.1029
Cancer[8]	19	0.82	8	1.39	0.2088

[1]taking anticoagulants for more than 30 days
[2]Hypertension (ICD-9-CM: 401-405, A code: A260, A269)
[3]Heart disease (ICD-9-CM: 410-429
[4]Hyperlipidemia (ICD-9-CM: 272.3, 272.4)
[5]Urinary stones (ICD-9-CM: 592, 594.1)
[6]Peptic ulcer (ICD-9-CM: 533, A code: A341)
[7]Anemia (ICD-9-CM: 280-285)
[8]Cancer (ICD-9-CM: 140-239)
chi-squared test comparing subjects between with and without *Flos carthami* group
*: P < 0.05; **: P < 0.01; ***: P < 0.001.

In univariate and multivariate Cox's proportional hazard regression models, the adjusted hazard ratio (HR) for bleeding disorders was 0.86 for the FC cohort relative to the non-FC cohort (P = 0.6094). Besides, adjusted HR of hypertension, heart disease, hyperlipidemia, urinary stones, peptic ulcer, anemia and cancer are not statistically significant between FC and non-FC cohort (Table 3).

Table 3. Cox model measured hazard ratio and 95% confidence intervals of bleeding disorders associated with *Flos carthami*

Characteristics	Bleeding no.	Crude			Adjusted model		
		HR	(95% CI)	p-value	HR	(95% CI)	*P* value
Flos carthami							
No	53	1.00	reference		1.00	reference	
Yes	15	1.03	(0.58-1.83)	0.9226	0.86	(0.47-1.56)	0.6094
Gender							
Male	41	1.00	reference		1.00	reference	
Female	27	0.38	(0.23-0.62)	<.0001***	0.87	(0.52-1.47)	0.6108
Age group							
18-39 years	7	1.00	reference		1.00	reference	
40-64 years	29	5.35	(2.34-12.21)	<.0001***	4.69	(2.01-10.94)	0.0003***
≥65 years	32	28.73	(12.68-65.13)	<.0001***	20.48	(8.36-50.17)	<.0001***
Comorbidity							
Hypertension							
No	45	1.00	reference		1.00	reference	
Yes	23	4.37	(2.65-7.23)	<.0001***	1.30	(0.69-2.42)	0.4163
Heart disease							
No	56	1.00	reference		1.00	reference	
Yes	12	4.81	(2.57-8.97)	<.0001***	1.46	(0.67-3.19)	0.3441
Hyperlipidemia							
No	66	1.00	reference		1.00	reference	
Yes	2	1.08	(0.26-4.4)	0.918	0.35	(0.08-1.46)	0.1492
Urinary stones							
No	64	1.00	reference		1.00	reference	
Yes	4	3.31	(1.21-9.09)	0.0202*	2.63	(0.93-7.42)	0.067
Peptic ulcer							
No	60	1.00	reference		1.00	reference	
Yes	8	3.37	(1.61-7.05)	0.0012**	1.81	(0.83-3.95)	0.1391
Anemica							
No	65	1.00	reference		1.00	reference	
Yes	3	2.22	(0.7-7.05)	0.1783	1.92	(0.56-6.58)	0.2969
Cancer							
No	66	1.00	reference		1.00	reference	
Yes	2	4.68	(1.15-19.12)	0.0317*	1.68	(0.38-7.35)	0.4934
Taking anticoagulants							
None or <30 days	53	1.00	reference		1.00	reference	
≥30 days	15	3.96	(2.23-7.02)	<.0001***	1.23	(0.61-2.49)	0.5701

Abbreviation: HR, hazard ratio; CI, confidence interval.
Adjusted HR: adjusted for age, gender, comorbidity and taking anticoagulants in Cox proportional hazards regression
*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

Table 4. Cox Proportional Hazard Regression Analysis for the risk of bleeding disorders -associated *Flos carthami* and anticoagulant users

Treatment		Event	Person years	IR[†]	Crude HR (95% CI)	Adjusted HR[¶] (95% CI)
Anticoagulants	*Flos carthami*					
No	No	43	14747.15	2.92	1(reference)	1(reference)
No	Yes	10	3809.42	2.63	0.89(0.45-1.78)	0.85(0.42-1.73)
Yes	No	10	863.66	11.58	3.93(1.98-7.83)***	1.23(0.56-2.70)
Yes	Yes	5	455.33	10.98	3.75(1.48-9.47)**	1.05(0.35-3.12)

[†]Abbreviation: IR, incidence rates, per 1,000 person-years; HR, hazard ratio; CI, confidence interval
[¶]Adjusted HR[†] represented adjusted hazard ratio: adjusted for age, gender and comobidity in Cox proportional hazards regression
*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

The joint effects of FC and anticoagulant use on the risk of bleeding disorders are presented in Table 4, with people with no histories of FC and anticoagulant use comprising the reference group. The risk of bleeding disorders for FC users was not significant (crude HR = 0.89, 95% confidence interval [CI] = 0.45–1.78, adjusted HR = 0.85,

95% CI = 0.42–1.73). People using anticoagulants only and those taking both FC and anticoagulants exhibited higher risks of bleeding disorders in the crude hazard models (crude HR = 3.93 [95% CI = 1.98–7.83] and crude HR = 3.75 [95% CI = 1.48–9.47], respectively), whereas significance was lost in the adjusted hazard models (adjusted HR = 1.23 [95% CI = 0.56–2.70] and adjusted HR = 1.05 [95% CI = 0.35–3.12], respectively). Additionally, the bleeding risk did not associated with the cumulative days of FC use (Table 5).

Table 5. Hazard Ratios and 95% confidence intervals of bleeding risk associated with cumulative use day of *Flos carthami*

	N	frequency of bleeding (n=274)	Hazard Ratio(95% CI)	
			Crude[1]	Adjusted[2]
Non- *Flos carthami* user	2308	53	1(reference)	1(reference)
Flos carthami user				
30-89 days	429	10	0.93(0.47-1.83)	0.53(0.19-1.47)
>90 days	148	5	1.30(0.52-3.26)	0.27(0.04-2.07)

[1] Relative hazard ratio; [2] represented adjusted hazard ratio: mutually adjusted for age, gender, hypertension, heart disease, hyperlipidemia, urinary stones, peptic ulcer, anemia and cancer in Cox proportional hazard regression.
*P < 0.05, **P < 0.01, ***P < 0.001.

4. Discussion

The results showed that the risks of GI bleeding, intracranial hemorrhage, and the hazard of blood transfusion were not increased by a Chinese anticoagulant herb FC. In Table 2, both FC and anticoagulants can be used to treat similar medical conditions [10,36], resulting in a higher frequency of anticoagulant use among FC users. Many studies revealed that FC can be used to treat hypertension, cardiac disease, hyperlipidemia, and urinary stones [13,37,38], and it is logical that these diseases were more common in the FC cohort in this study. However, there was a high risk of bleeding events in people taking anticoagulants only, but the risk was not further increased among participants taking both anticoagulants and FC. This implies that most bleeding events were caused by western anticoagulant use.

The crude HR of bleeding disorders in females relative to the reference group (males) was 0.38 (P < 0.0001), but the adjusted HR did not indicate significance. Hence, there was no difference in the risk of bleeding events between males and females after adjusting for age, comorbidities, and anticoagulant use via Cox proportional hazards regression. The data also illustrated that the risk of bleeding disorders increased with increasing age, as the adjusted HR for bleeding disorders for participants aged ≥65 years and 40-64 years were 20- and 4.7-fold higher, respectively, than that for participants aged 18-39 years. The results were similar to some studies suggesting a trend of increased risk of bleeding disorders among the elderly [20,22].

There was no significant difference in the risk of bleeding disorders between anticoagulant use for less than 30 days (or no anticoagulant use at all) and anticoagulant use for 30 days or more, and likewise, the study suggested that the incidence of intracranial hemorrhage was low among patients taking warfarin prior to head trauma [24], although some studies revealed adverse effects of anticoagulant use among patients with brain injuries [28,30]. In Table 4, the use of FC and anticoagulants alone or in combination did not increase the risks of GI bleeding, intracranial hemorrhage, and blood transfusion. Although bleeding was more likely among warfarin users [39], supratherapeutic anticoagulation is associated with decreased mortality [40]. The association between anticoagulant use and bleeding disorder risk and mortality should be a focus of further research. Moreover, a prior study indicated that FC injection inhibits drug metabolism cytochrome P 450 enzymes in the rat model [41]. Drug-herb interactions between TCM and pharmaceutical products will be a focus of our future research.

In addition to its medical use in Asia, FC is also used as a food additive in the Middle East and Mediterranean Sea regions. There has been extensive debate about the cytotoxic effects and safety of FC [42,43,44]. In experiments utilizing water-soluble FC injection, the agent had no toxicological effects on male or female rats, and no adverse effects were observed at a high dose level (>0.5 mL/animal/day) [43,44]. The safety level (<0.8 mg/kg/day) equate FC doses of 7.2 and 4.8 g/day, respectively, in a person weighing 60 kg. Traditional Chinese physicians generally prescribe FC at a dose of 1–2 g/day to patients in Taiwan, whereas doses in excess of 3 g/day are rarely prescribed. Study data indicate that FC use at these doses is not harmful.

Our study has several limitations. First, participants were identified using a diagnostic code in a database, introducing the possibility of misclassification because of coding errors or misdiagnosis. Second, some potential risk factors were not included in our analyses because these data were not available. Third, the follow-up period may not have been sufficiently long to detect development of bleeding complications. Finally, since this population-based cohort study was conducted with a NHIRD, the information of quantity of FC used and the diets of the populations was unavailable. Although we did not show the quantity of FC, FC is always used with small quantity around 0.5-2.0 gram a day in clinical therapy. Further research is needed to determine the possible pathogenic mechanisms between Chinese herbal anticoagulant prescribed in bleeding complications are necessary.

5. Conclusions

The risks of GI bleeding, intracranial hemorrhage, and blood transfusion were not higher among FC users than among non-FC users. Most drug-related bleeding events were caused by western anticoagulant use.

Acknowledgements

The authors declare that they have no conflict of interest. This study is supported in part by 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 104-2325-B-039-005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan. Taiwan Ministry of Science and Technology (MOST 104-2320-B-039-016-MY3), China Medical University Hospital (DMR-105-048), and CMU under the Aim for Top University Plan of the Taiwan Ministry of Education (A-5-2-A). Y.H.C. and W.C.C contributed equally to this study.

References

[1] M. Mariassyova, "Antioxidant activity of some herbal extracts in rapeseed and sunflower oils," *Journal of Food and Nutrition Research,* 45 (3). 104-109. 2006.

[2] O. Demirkol, and A. Cagri-Mehmetoglu, "Biologically important thiols in various organically and conventionally grown vegetables," *Journal of Food and Nutrition Research,* 47 (2). 77-84. 2008.

[3] H. J. Suh, and S. Choi, "Risk assessment of daily intakes of artificial colour additives in food commonly consumed in Korea," *Journal of Food and Nutrition Research,* 51 (1). 13-22. 2012.

[4] D. H. Yang, X. L. Ren, F. Xu, X. Q. Ma, G. X. Liu, C. H. Li, C. Li, and S. Q. Cai, "Absorptive constituents and their metabolites in drug-containing urine samples from Wuzhishan miniature pigs orally administered with Buyang Huanwu decoction," *Journal of Natural Medicines,* 68 (1). 11-21. 2014.

[5] N. Wiseman, "Introduction to English Terminology of Chinese Medicine," *Ho-Chi Book Publishing Company*. 2003.

[6] Q. Mu, P. Liu, X. Hu, H. Gao, X. Zheng, and H. Huang, "Neuroprotective effects of Buyang Huanwu decoction on cerebral ischemia-induced neuronal damage," *Neural Regen Res,* 9 (17). 1621-1627. 2014.

[7] E. H. Liu, L. W. Qi, Y. B. Peng, X. L. Cheng, Q. Wu, P. Li, and C. Y. Li, "Rapid separation and identification of 54 major constituents in Buyang Huanwu decoction by ultra-fast HPLC system coupled with DAD-TOF/MS," *Biomedical Chromatography,* 23 (8). 828-842. 2009.

[8] J. Kim, J. Woo, J. H. Lyu, H. H. Song, H. S. Jeong, K. T. Ha, J. Y. Choi, C. W. Han, K. S. Ahn, S. R. Oh, R. T. Sadikot, K. H. Kim, and M. Joo, "Carthami Flos suppresses neutrophilic lung inflammation in mice, for which nuclear factor-erythroid 2-related factor-1 is required," *Phytomedicine,* 21 (4). 470-478. 2014.

[9] P. H. Nie, L. Zhang, W. H. Zhang, W. F. Rong, and J. M. Zhi, "The effects of hydroxysafflor yellow A on blood pressure and cardiac function," *Journal of Ethnopharmacology,* 139 (3). 746-750. 2012.

[10] L. Liu, J. A. Duan, Y. Tang, J. Guo, N. Yang, H. Ma, and X. Shi, "Taoren-Honghua herb pair and its main components promoting blood circulation through influencing on hemorheology, plasma coagulation and platelet aggregation," *Journal of Ethnopharmacology,* 139 (2). 381-387. 2012.

[11] S. Y. Wu, K. M. Man, J. L. Shen, H. Y. Chen, C. H. Chang, F. J. Tsai, W. T. Hsieh, D. Winardi, Y. J. Lee, K. S. Tsai, Y. N. Lin, Y. H. Chen, and W. C. Chen, "Effect of Flos carthami Extract and alpha 1-Adrenergic Antagonists on the Porcine Proximal Ureteral Peristalsis," *Evidence-Based Complementary and Alternative Medicine,* 2014. 437803. 2014.

[12] J.-C. Wu, Z. L. Yub, W. F. Fong, and Y. Q. Shia, "Chemotherapeutic activities of Carthami Flos and its reversal effect on multidrug resistance in cancer cells," *African Journal of Traditional, Complementary and Alternative Medicines,* 10 (4). 2013.

[13] W. C. Lin, M. T. Lai, H. Y. Chen, C. Y. Ho, K. M. Man, J. L. Shen, Y. J. Lee, F. J. Tsai, Y. H. Chen, and W. C. Chen, "Protective effect of Flos carthami extract against ethylene glycol-induced urolithiasis in rats," *Urological Research,* 40 (6). 655-661. 2012.

[14] R. Miyaoka, and M. Monga, "Use of traditional Chinese medicine in the Management of Urinary Stone Disease," *International Braz J Urol,* 35 (4). 396-405.

[15] S. Y. Wu, J. L. Shen, K. M. Man, Y. J. Lee, H. Y. Chen, Y. H. Chen, K. S. Tsai, F. J. Tsai, W. Y. Lin, and W. C. Chen, "An emerging translational model to screen potential medicinal plants for nephrolithiasis, an independent risk factor for chronic kidney disease," *Evidence-Based Complementary and Alternative Medicine,* 2014. 972958. 2014.

[16] A. N. Barkun, M. Bardou, E. J. Kuipers, J. Sung, R. H. Hunt, M. Martel, and P. Sinclair, "International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding," *Ann Intern Med,* 152. 101-113. 2010.

[17] J. D. Lewis, W. B. Bilker, C. Brensinger, J. Farrar, and B. L. Strom, "Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s," *The American Journal of Gastroenterology,* 97 (10). 2540-2549. 2002.

[18] L. E. Targownik, and A. Nabalamba, "Trends in management and outcomes of acute nonvariceal upper gastrointestinal bleeding: 1993-2003," *Clinical Gastroenterology and Hepatology,* 4 (12). 1459-1466. 2006.

[19] A. Lassen, J. Hallas, and O. B. Schaffalitzky de Muckadell, "Complicated and uncomplicated peptic ulcers in a Danish county 1993-2002: a population-based cohort study," *American Journal of Gastroenterology,* 101 (5). 945-953. 2006.

[20] Y. Zhao, and W. Encinosa, "Hospitalizations for Gastrointestinal Bleeding in 1998 and 2006," *Agency for Healthcare Research and Quality*. 2008.

[21] M. Vanleerdam, E. Vreeburg, E. Rauws, A. Geraedts, J. Tijssen, J. Reitsma, and G. Tytgat, "Acute Upper GI Bleeding: Did Anything Change?Time Trend Analysis of Incidence and Outcome of Acute Upper GI Bleeding Between 1993/1994 and 2000," *The American Journal of Gastroenterology,* 98 (7). 1494-1499. 2003.

[22] B. S. Sheu, C. Y. Wu, M. S. Wu, C. T. Chiu, C. C. Lin, P. I. Hsu, H. C. Cheng, T. Y. Lee, H. P. Wang, and J. T. Lin, "Consensus on control of risky nonvariceal upper gastrointestinal bleeding in Taiwan with National Health Insurance," *Biomed Res Int,* 2014. 563707. 2014.

[23] J. J. Sung, F. K. Chan, M. Chen, J. Y. Ching, K. Y. Ho, U. Kachintorn, N. Kim, J. Y. Lau, J. Menon, A. A. Rani, N. Reddy, J. Sollano, K. Sugano, K. K. Tsoi, C. Y. Wu, N. Yeomans, N. Vakil, K. L. Goh, and G. Asia-Pacific Working, "Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding," *Gut,* 60 (9). 1170-1177. 2011.

[24] J. Miller, L. Lieberman, B. Nahab, G. Hurst, J. Gardner-Gray, A. Lewandowski, S. Natsui, and J. Watras, "Delayed intracranial hemorrhage in the anticoagulated patient: A systematic review," *J Trauma Acute Care Surg,* 79 (2). 310-313. 2015.

[25] A. M. Holbrook, J. A. Pereira, R. Labiris, H. McDonald, J. D. Douketis, M. Crowther, and P. S. Wells, "Systematic overview of warfarin and its drug and food interactions," *Arch Intern Med,* 165. 1095-1106. 2005.

[26] L. A. Dossett, J. N. Riesel, M. R. Griffin, and B. A. Cotton, "Prevalence and implications of preinjury warfarin use: an analysis of the National Trauma Databank," *Archives of Surgery,* 146 (5). 565-570. 2011.

[27] A. A. Mina, H. A. Bair, G. A. Howells, and P. J. Bendick, "Complications of preinjury warfarin use in the trauma patient," *Journal of Trauma,* 54 (5). 842-847. 2003.

[28] A. Lavoie, S. Ratte, D. Clas, J. Demers, L. Moore, M. Martin, and E. Bergeron, "Preinjury Warfarin Use Among Elderly Patients With Closed Head Injuries in a Trauma Center," *The Journal of Trauma: Injury, Infection, and Critical Care,* 56 (4). 802-807. 2004.

[29] A. A. Mina, J. F. Knipfer, D. Y. Park, H. A. Bair, G. A. Howells, and P. J. Bendick, "Intracranial complications of preinjury anticoagulation in trauma patients with head injury," *Journal of Trauma,* 53 (4). 668-672. 2002.

[30] A. Karni, R. Holtzman, T. Bass, G. Zorman, L. Carter, L. Rodriguez, V. J. Bennett-Shipman, and L. Lottenberg, "Traumatic head injury in the anticoagulated elderly patient," *The American Surgeon,* 67 (11). 1098-1100. 2001.

[31] J. Franko, K. J. Kish, B. G. O'Connell, S. Subramanian, and J. V. Yuschak, "Advanced age and preinjury warfarin anticoagulation increase the risk of mortality after head trauma," *Journal of Trauma,* 61 (1). 107-110. 2006.

[32] M. Kalina, G. Tinkoff, A. Gbadebo, P. Vener, and G. Fulda, "A protocol for the rapid normalization of INR in trauma patients

with intracranial hemorrhage on prescribed warfarin therapy," *The American Surgeon,* 74 (9). 858-861. 2008.

[33] T. Y. Wu, A. Majee, and K. N. Kuo, "An overview of the healthcare system in Taiwan," *London Journal of Primary Care,* 3. 115-119. 2010.

[34] "Universal Health Coverage in Taiwan." 2012.

[35] L. Chen, W. Yip, M. C. Chang, H. S. Lin, S. D. Lee, Y. L. Chiu, and Y. H. Lin, "The effects of Taiwan's National Health Insurance on access and health status of the elderly," *Health Econ,* 16 (3). 223-242. 2007.

[36] Y. Lu, Y. L. Hu, X. F. Kong, and D. Y. Wang, "Selection of component drug in activating blood flow and removing blood stasis of Chinese herbal medicinal formula for dairy cow mastitis by hemorheological method," *Journal of Ethnopharmacology,* 116 (2). 313-317. 2008.

[37] Y. Chen, M. Liu, T. Zhao, B. Zhao, L. Jia, Y. Zhu, B. Zhang, X. Gao, G. Li, X. Li, R. Xiang, J. Han, and Y. Duan, "Danhong injection inhibits the development of atherosclerosis in both Apoe(-)/(-) and Ldlr(-)/(-) mice," *Journal of Cardiovascular Pharmacology,* 63 (5). 441-452. 2014.

[38] L. G. Yan, J. S. Ruan, L. Zhang, F. T. Fan, F. Zhang, A. Y. Wang, S. Z. Zheng, L. Zeng, W. L. Li, and Y. Lu, "Effect of aqueous extracts of several kinds of herbs on human platelet aggregation and expression of P-selectin in vitro," *Chinese Journal of Integrative Medicine,* 21 (4). 286-290. 2015.

[39] B. Roca, and M. Roca, "The new oral anticoagulants: Reasonable alternatives to warfarin," *Cleveland Clinic Journal of Medicine,* 82 (12). 847-854. 2015.

[40] J. Irwin, R. Ferguson, F. Weilert, and A. Smith, "Supratherapeutic anticoagulation at presentation is associated with reduced mortality in nonvariceal upper gastrointestinal hemorrhage," *Endosc Int Open,* 2 (3). E148-152. 2014.

[41] G. Liu, Y. Liu, R. Liu, F. Dong, and Z. Zhang, "Effects of Flos carthami on CYP2D6 and on the Pharmacokinetics of Metoprolol in Rats," *Evidence-Based Complementary and Alternative Medicine,* 2011. 207076. 2011.

[42] M. Nobakht, M. Fattahi, M. Hoormand, I. Milanian, N. Rahbar, and M. Mahmoudian, "A study on the teratogenic and cytotoxic effects of safflower extract," *Journal of Ethnopharmacology,* 73 (2000). 453-459. 2000.

[43] Y. M. Choi, D. J. Jung, S. H. Kim, J. U. Kim, and T. H. Yook, "Repeated Intramuscular-dose Toxicity Test of Watersoluble Carthami Flos (WCF) Pharmacopuncture in Sprague-Dawley Rats," *J Pharmacopuncture,* 18 (1). 36-43. 2015.

[44] D. J. Jung, Y. M. Choi, S. H. Kim, J. U. Kim, and T. H. Yook, "Single Intravenous-dose Toxicity of Water-soluble Carthami-flos Pharmacopuncture (WCF) in Rats," *J Pharmacopuncture,* 17 (3). 31-39. 2014.