


Literature Review of Traditional Chinese Medicine Herbs–Induced Liver Injury From an Oncological Perspective With RUCAM

Integrative Cancer Therapies
Volume 18: 1–13
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1534735419869479
journals.sagepub.com/home/ict


Hei Ching Chow¹ , Tsz Him So, BChinMed, MBBS, FRCR¹,
Horace Cheuk Wai Choi, PhD¹, and Ka On Lam, MBBS, FRCR¹

Abstract

Traditional Chinese medicine (TCM) herbs are commonly regarded to be safe with minimal toxicities in Chinese communities. Cancer patients who are receiving Western oncology therapy often concurrently take TCM herbs for anticancer and symptom relief purposes. We performed a literature review for current evidence on TCM herb–induced liver injury from an oncological perspective. A literature search on PubMed was performed to identify publications regarding TCM herbs and concoctions with hepatoprotective or hepatotoxic properties. Lists of commonly used herbs and their causality levels were compiled. In view of the wide range of evidence available, cases assessed by the well-established RUCAM (Roussel Uclaf Causality Assessment Method) algorithm were categorized as the highest level of evidence. More than one case of TCM herb–induced liver injury was confirmed by RUCAM in the following herbs and concoctions: Lu Cha (*Camellia sinensis*), Bai Xian Pi (*Dictamnus dasycarpus*), Tu San Qi (*Gynura segetum*), Jin Bu Huan (*Lycopodium serratum*), He Shou Wu (*Polygoni multiflora*), Ge Gen (*Pueraria lobata*), Dan Lu Tong Du tablet, Shou Wu Pian, Xiao Chai Hu Tang, Xiao Yin pill, and Yang Xue Sheng Fa capsule. Finally, TCM with anticancer or symptom relief uses were discussed in detail with regard to their hepatotoxic or hepatoprotective properties.

Keywords

traditional Chinese medicine, liver toxicity, hepatotoxicity, cancer, oncology, Chinese herbal medicine, RUCAM

Submitted June 17, 2019; revised July 7, 2019; accepted July 16, 2019

Introduction

Multiple studies have shown that there is widespread use of traditional Chinese medicine (TCM) among Chinese patients as an adjuvant to Western medicine in cancer treatment.^{1–5} Another study revealed that the self-care of Chinese cancer patients has been heavily influenced by the TCM philosophy.⁶ In addition to taking herbal medicines prescribed by Chinese medicine practitioners, it is also common for the general public to use proprietary Chinese medicine on their own or add herbs to meals and soups. A study found that over half of the Hong Kong cancer patients surveyed used at least one form of TCM. Furthermore, 60% of these patients who were receiving chemotherapy concurrently used TCM.⁷ According to a Taiwanese survey, 69% of respondents thought that TCM is mild and has no ill effects at all.⁸ TCM herbs and concoctions, like any drug, also have side effects and toxicities.

Many oncologists do not encourage the concurrent use of TCM due to the potential of having adverse interactions between Chinese and Western drugs that may lead to hepatotoxicity. There have been numerous reports of liver injury caused by TCM herbs and concoctions. However, the establishment of causality varies in these reports. A typical example of TCM-induced liver toxicity is He Shou Wu, which is a popular herb for preventing hair loss and aging. A study found that only 30.6% of literature case reports demonstrate a high probability of

¹Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

Corresponding Author:

Tsz Him So, Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 1/F Professorial Block, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong.
Email: sth495@hku.hk



He Shou Wu–induced liver injury causality.⁹ The causality between TCMs and drug-induced liver injury was ascertained by various methods, such as by patient recall, clinical suspicion, exclusion, and algorithms. It is important to note the complexity and difficulty in establishing causality for TCM herbs. One difficulty is due to polypharmacy as TCM is rarely used as a single herb, and TCM may sometimes be used concomitantly with Western drugs. Another difficulty is contamination by heavy metals.¹⁰ Evidence available in case reports, case series, and reviews may not be complete. If these confounders are not excluded, misdiagnosis and overreporting may occur.

Hence, there is a need to categorize the cases in the existing literature into different evidence levels of causality. Focus should be given to hepatotoxic TCM for which clear evidence has been demonstrated by standardized causality assessment algorithms. RUCAM (Roussel Uclaf Causality Assessment Method), or its previous synonym CIOMS (Council for International Organizations of Medical Sciences), is the most commonly used causality instrument for drug-induced liver toxicity.¹¹ RUCAM is used to assess causality quantitatively, by applying numerical weighting to key features such as chronology and risk factors, and it generates an overall score to indicate the probability of causality. The RUCAM scale ranges as follows: 0, excluded; 1 to 2, unlikely; 3 to 5, possible; 6 to 8, probable; and ≥ 9 , highly probable.¹²

Furthermore, not all TCM herbs and concoctions cause hepatotoxicity. In fact, some of them have hepatoprotective effects against drug-induced liver injury, such as chemotherapy-induced hepatotoxicity.

In this article, we present a review of the current literature to identify potentially hepatotoxic or hepatoprotective TCM that cancer patients may concurrently use with Western systemic therapies, and stratify them using causality levels to offer easier interpretation.

Methodology

Data Sources and Searches

We carried out a systematic search of the PubMed database on March 11, 2019, to identify publications of laboratory findings, case reports, case series, and review articles of TCM-induced hepatotoxicity. By using Medical Subject Headings, English articles that were associated with the terms “Chemical and Drug-Induced Liver Injury” and “Medicine, Chinese Traditional” were selectively included. Our search yielded 64 results.

Exclusion of Publications

Publications were excluded by the following criteria. Publications were excluded if

- They were unrelated to TCM-induced hepatotoxicity or hepatoprotection, or
- Access to the full article could not be obtained, or
- No specific TCM herbs or concoctions were named, or
- No significant results were directly shown with specific TCM herbs or concoctions.

As a result, 14 publications were excluded from this review.

Data Analysis

Data Extraction. Fifty publications were analyzed. Individual herbs and herbal concoctions were identified. The scientific names of each herb and its corresponding Chinese name were determined. As a single TCM herb could have different scientific names (eg, *Polygoni multiflori* vs *Polygonum multiflorum* Thunb), results were grouped according to the Chinese name of the herb. The publications were then analyzed to yield the number of clinical cases and causality.

Duplication of Data. The references of these 50 publications were carefully inspected. There were case reports, case series, and reviews referring to the same event of hepatotoxicity caused by a certain TCM herb or concoction. In particular, 3 systematic reviews were published by the same author in 3 consecutive years, and each systematic review cited cases from the previous review. Duplicated data were discarded in this review.

Exclusion of TCM Herbs or Concoctions. If the publication failed to provide any of the aforementioned data (eg, number of cases), the reference lists of the primary and review articles were scanned. If the primary source could not be accessed, the data of the individual herb or concoction were also excluded.

Levels of Causality

Hepatotoxic herbs or concoctions. In view of the wide range of clinical causality ascertainment methods in the literature, as well as the fact that laboratory findings do not directly infer clinical significance, a stratified level of causality was devised in order to provide a clearer and more clinically oriented picture.

Entries of hepatotoxic herbs or herbal concoctions found from the publications were categorized into 1 of the 4 following levels according to the following description:

Level	Context	Description
1	Nonclinical	The publication shows that certain TCM herbs/concoctions or their chemicals lead to hepatotoxicity in a laboratory setting. The experiments were conducted with animals or human cells.
2	Clinical	The publication suspected certain TCM herbs/concoctions would lead to hepatotoxicity, or associated certain TCM herbs/concoctions with hepatotoxicity. No causality was established.
3	Clinical	The publication suggested that certain TCM herbs/concoctions caused hepatotoxicity. Causality was ascertained by RUCAM in which cases were graded “possible,” or by other assessment algorithms like the positive reexposure test.
4	Clinical	The publication suggested that certain TCM herbs/concoctions caused hepatotoxicity. Clear causality was ascertained by RUCAM, in which cases were graded “probable” or higher. ¹³

Hepatoprotective herbs or concoctions. After excluding uncommonly used hepatoprotective herbs and herbal concoctions, only nonclinical ones remained; hence, they were not graded by causality levels.

Results

Lists of herbs and concoctions that were hepatotoxic or hepatoprotective, their respective causality levels, and number of cases are compiled in Tables 1 to 5.^{9,13-46}

We found 20, 17, 34, and 27 individual herbs that were graded level 4, 3, 2, and 1 for their causality toward liver injury, respectively. For herbal concoctions, we found 6, 10, 7, and 2 concoctions that were graded level 4, 3, 2, and 1, respectively. There were in total 21 herbs or concoctions that were hepatoprotective in laboratory settings. Using RUCAM, clear causality (level 4) was established in 194 cases of TCM-induced liver toxicity.

Discussion

TCM for Symptom Relief and Body Enhancement

He Shou Wu (何首烏, *Polygoni multiflori*) is traditionally used for treating premature whitening of hair, dizziness, and insomnia due to the insufficiency of essence and blood.⁴⁷ This makes He Shou Wu a popular choice among cancer patients to counter the side effects of chemotherapy such as alopecia. According to our results, there were 80 cases reaching level 4 (clearly established causality), 147 cases reaching level 3 (possible causality), and 516 cases attaining level 2 (clinical suspicion). Furthermore, when He Shou Wu was coadministered with other drugs as herbal concoctions, there were 37 cases that reached level 4. Therefore, there was clear evidence that He Shou Wu could cause liver injury.

In TCM, Chuan Lian Zi (川楝子, *Melia toosendan*) is used for relieving pain,⁴⁸ and it is often used by cancer patients for pain control and to “relieve liver Qi congestion,”

which is common among breast and liver cancer patients according to TCM theory. However, Chuan Lian Zi is known to have a slightly toxic property.⁴⁹ Our search results in a case (level 4) of Chuan Lian Zi–induced liver injury.

Ren Shen (人參, *Panax ginseng*) has gained popularity in recent years. The annual world ginseng production was estimated to be 80 080 tons, and its global consumption has risen steadily over the years. Ginseng is being marketed as a natural health food and various forms are available.⁵⁰ Cancer patients take Ren Shen prepared in the form of tea, capsules, or as an ingredient in soup in the hope of increasing their “inner resistance.”⁶ Ren Shen could be used for restoring Qi. It can treat severe vomiting, fatigue, diarrhea, shortness of breath, fatigue, feeble pulse, extreme weakness after severe disease, or prolonged illness.⁴⁷ During chemotherapy, patients might experience the above symptoms and may use this herb. Our review found a case of possible (level 3) hepatotoxicity caused by intravenous wild ginseng pharmacopuncture and 6 cases of suspected liver injury (level 2) caused by Ren Shen. Hence, further research should be done to confirm the causality of liver injury caused by this popular herb.

San Qi (三七, *Panax notoginseng*) is a herb used to arrest bleeding and remove blood stasis in TCM. It is also known to be helpful in reducing swelling and relieving pain.⁴⁸ Hence, this herb might be used to reduce the pain caused by the tumor. According to laboratory findings, it was suggested that it has hepatoprotective effects. Unfortunately, another similarly named herb named Tu San Qi (土三七), or *Radix Gynuræ Segeti*, has been proven to induce hepatic sinusoidal obstruction syndrome/veno-occlusive disease.⁵¹ Contrary to the hepatoprotective San Qi, Tu San Qi led to 4 cases of liver injury (level 4). Hence, caution must be taken to avoid misidentification.

Chai Hu (柴胡, *Bupleurum falcatum*) is an important component in Xiao Chai Hu Tang (小柴胡湯; XCHT). XCHT is a commonly used concoction to treat Shaoyang disease with symptoms such as chills and fever, nausea and dizziness, restlessness, fullness, discomfort at the chest, and

Table 1. TCM Herbs That Were Assessed by RUCAM to Demonstrate Clear Causality of Hepatotoxicity.

中藥名	Commonly Known as	Scientific Name	Level of Causality	No. of Cases
刺五加	Ci Wu Jia	<i>Acanthopanax senticosus</i> ^{13,14}	4	1
澤瀉	Ze Xie	<i>Alisma orientalis</i> ¹³⁻¹⁵	4	1
蘆薈	Aloe Vera	<i>Aloe perfoliata</i> ¹⁶	4	1
獨活	Du Huo	<i>Angelica archangelica</i> ¹³⁻¹⁵	4	1
茵陳蒿	Yin Chen Hao	<i>Artemisia capillaris</i> ^{14,15}	4	1
綠茶	Lu Cha/Green tea/Chaso	<i>Camellia sinensis</i> ¹³⁻¹⁵	4	28
決明子	Jue Ming Zi	<i>Cassia obtusifolia</i> ^{13,14}	4	1
珠果黃堇	Zh Guo Huang Jin, Hwang Geun Cho	<i>Corydalis speciose</i> ^{13,14,16}	4	1
柘木	Zhe Mu	<i>Cudrania tricuspidata</i> ¹⁶	4	1
白鮮皮	Bai Xian Pi	<i>Dictamnus dasycarpus</i> ^{13,14,16}	4	7
甘草	Gan Cao, Liquorice	<i>Glycyrrhiza uralensis</i> ¹³⁻¹⁵	4	1
土三七	Tu San Qi	<i>Gynura segetum</i> /Radix <i>Gynurae Segeti</i> ¹³⁻¹⁵	4	4
枳椇子	Ji Ju Zi, Jiguja	<i>Hovenia dulcis</i> ¹³⁻¹⁵	4	1
金不換	Jin Bu Huan	<i>Lycopodium serratum</i> ^{13,14}	4	3
川楝子	Chuan Lian Zi	<i>Melia toosendan</i> ^{13,14}	4	1
薄荷	Bo He	<i>Mentha haplocalyx</i> ^{13,14}	4	1
何首烏	He Shou Wu, Hoshouwu	<i>Polygoni multiflori</i> /Polygoum <i>multiflorum</i> ^{9,13-16}	4	80
葛根	Ge Gen	<i>Pueraria lobata</i> ¹³⁻¹⁵	4	2
大黃	Da Huang	<i>Rheum palmatum</i> ^{13,14}	4	1
菝葜	Ba Qia	<i>Smilacis Chinae Radix</i> ¹⁶	4	1

Abbreviations: TCM, traditional Chinese medicine; RUCAM, Roussel Uclaf Causality Assessment Method.

dry throat.⁴⁸ Cancer patients may experience neutropenic fever, and XCHT is a common folk remedy that might be taken. Our results found that there were 4 cases of XCHT reaching level 4, while Chai Hu had 28 cases reaching level 2. On the other hand, Si Ni San, a concoction containing Chai Hu, is used to treat chronic hepatitis.⁴⁸ Si Ni San was found to be hepatoprotective in laboratory settings. We hypothesize that this could be due to the interaction between different herbs in concoctions. When herbs containing hepatotoxic constituents are boiled with other herbs, it is possible that new compounds that are nonhepatotoxic are formed.

Another herb that showed conflicting results was Yin Chen Hao (茵陳蒿, *Artemisia capillaris*). Our literature search found that this herb causes liver injury, with 1 case of level 4 and 7 cases of level 2. On the contrary, Yin Chen Hao is used to treat jaundice in TCM. Oncology patients may take this herb to reduce jaundice. A concoction that uses Yin Chen Hao as a major herb, named Yin Chen Hao Tang (茵陳蒿湯), is also used for treating jaundice and diseases such as acute infectious icterohepatitis, acute cholecystitis, cholelithiasis, and leptospirosis in TCM. Our literature search found that laboratory findings suggesting Yin Chen Hao Tang has hepatoprotective properties. We postulate that as TCM herbs are rarely prescribed as a single herb, the other herbs that are prescribed concurrently may mitigate the hepatotoxic effects of Yin Chen Hao. Thus, in

the form of a concoction, Yin Chen Hao Tang demonstrates hepatoprotective properties.

Wu Wei Zi (五味子, *Schisandra chinensis*) is found to be hepatoprotective in our literature search. It is also known to be effective in lowering transaminase levels in those suffering from chronic hepatitis.⁴⁸ Hence, this herb may be taken by cancer patients to reduce the liver toxicity of systemic therapies and improve their liver function.

Bai Shao (白芍, *Radix Paeoniae Alba*) is known to nourish the liver and treat diarrhea, dysentery, and pain.⁴⁸ This herb may be taken by cancer patients in hopes of improving their liver function. The results of our review echoed with its TCM use, as it was found to have hepatoprotective properties in the laboratory setting.

TCM With Anticancer Properties

Bai Xian Pi (白鮮皮, *Dictamnus dasycarpus*) has been found to contain chemical constituents with cytotoxic properties.⁵² One study showed the inhibitory effect of one of its chemical constituents on human breast cancer cells. Thus, it may be prescribed by TCM practitioners to patients for anticancer purposes.⁵³ However, our review found that Bai Xian Pi could cause hepatotoxicity, which could probably be explained by its cytotoxic properties. We found 7 and 32 cases that reached level 4 and 3, respectively.

Table 2. TCM Concoctions That Were Assessed by RUCAM to Demonstrate Clear Causality of Hepatotoxicity.

中成藥/方劑名稱	TCM Concoctions	Level of Causality	No. of Cases
丹鹿通督片: 丹參、鹿角膠、黃芪、延胡索、杜仲	Dan Lu Tong Du tablet: <i>Salvia miltiorrhiza</i> , <i>Cervi cornus Colla</i> , <i>Astragalus membranaceus</i> , <i>Corydalis yanhusuo</i> , <i>Eucommia ulmoides</i> ¹⁷	4	8
首烏片: 牛膝、菟絲、鱧腸、女槿、忍冬、桑白皮、何首烏、補骨脂、地黃、金櫻子、芝麻、豨薟	Shou Wu Pian: <i>Achyranthes bidentata</i> , <i>Cuscuta chinensis</i> , <i>Eclipta prostrata</i> , <i>Ligustrum lucidum</i> , <i>Lonicera japonica</i> , <i>Morus alba</i> , <i>Polygonum multiflorum</i> , <i>Psoralea corylifolia</i> , <i>Rehmannia glutinosa</i> , <i>Rosa laevigata</i> , <i>Sesamum indicum</i> , <i>Siegesbeckia orientalis</i> ^{13,14}	4	28
小柴胡湯: 柴胡、人參、甘草、半夏、黃芩、薑和大棗	Syosaikoto/Xiao Chai Hu Tang: <i>Bupleurum falcatum</i> , <i>Ginseng</i> , <i>Glycyrrhiza glabra</i> , <i>Pinellia tuber</i> , <i>Scutellaria baicalensis</i> , <i>Zingiber officinale</i> , <i>Zizyphus jujuba</i> ^{13,14}	4	4
消銀膠囊: 地黃、芍藥、白芍、當歸、苦參、金銀花、玄參、牛蒡子、蟬蛻、黃芩、防風、大青葉、紅花	Xiao Yin pill: <i>Rehmannia glutinosa</i> , <i>Paeonia suffruticosa</i> , <i>Paeonia lactiflora</i> , <i>Angelica sinensis</i> , <i>Sophora flavescens</i> , <i>Lonicera japonica</i> , <i>Scrophularia ningpoensis</i> , <i>Arctium lappa</i> , <i>Periostracum cicadae</i> , <i>Cortex dictamni</i> , <i>Saposhnikovia divaricata</i> , <i>Folium isatidis</i> , <i>Carthamus tinctorius</i> ¹⁷	4	6
養血生髮膠囊: 熟地黃、當歸、羌活、木瓜、川芎、白芍、菟絲子、天麻、制何首烏	Yang Xue Sheng Fa capsule: <i>Radix rehmanniae preparata</i> , <i>Angelica sinensis</i> , <i>Notopterygium incisum</i> , <i>Chaenomeles speciosa</i> , <i>Ligusticum chuanxiong</i> , <i>Paeonia lactiflora</i> , <i>Semen cuscutae</i> , <i>Gastrodia elata</i> , <i>Radix polygoni multiflori preparata</i> ¹⁷	4	9
熱多寒少湯加大黃: 大黃、葛根、黃芩、細葉蘘本、萊菔子、桔梗、升麻、白芷	Yeoldahanso-tang plus Rheum rhabarbarum: <i>Rhei Radix et Rhizomaa</i> , <i>Pueraria thunbergiana</i> Bentham, <i>Scutellariae Radix</i> , <i>Ligusticum tenuissimum</i> Kitagawa, <i>Raphani Semen</i> , <i>Platycodonis Radix</i> , <i>Cimicifuga heracleifolia</i> , <i>Angelicae Dahuricae Radix</i> ¹⁶	4	1

Abbreviations: TCM, traditional Chinese medicine; RUCAM, Roussel Uclaf Causality Assessment Method.

An interesting finding was *Camellia sinensis* (綠茶), commonly known as green tea, had 28 cases reaching level 4. In contrast, previous research has shown that green tea extract has antioxidant and antihepatotoxic properties.⁵⁴ Green tea was also reported to have anticancer properties. A review suggested green tea has anti-breast cancer activity by adjusting cell signaling pathways.⁵⁵ Its seeds were also found to have inhibitory effects on human ovarian cancer cells.⁵⁶ An extract also showed inhibitory effects on the growth of colorectal cancer cells.⁵⁷ We hypothesize that while there are certain chemical constituents that may be beneficial to health, green tea may also contain hepatotoxic constituents and may lead to liver injury when taken in large quantities.

Huang Yao Zi (黃藥子, *Dioscorea bulbifera* L) is traditionally used to treat goiter, hyperthyroidism, and tumors,⁴⁸ and it could be prescribed to patients with thyroid cancer. However, it is known that overdose or long-term usage could lead to liver damage.⁵⁸ Surprisingly, no clinical cases of related hepatotoxicity were found in our literature search, only laboratory findings showed the potential of liver injury

caused by this herb. This could be explained by the decreasing popularity and cautious use of this herb in clinical TCM practice nowadays.

Our review found 1 case of Huang Qin (黃芩 *Scutellaria baicalensis*) that reached level 3 and 22 cases of level 2. This potentially hepatotoxic herb has been found to have anti-cancer properties, its chemical constituents were found to be cytotoxic to a broad range of human cancer cells, including brain tumor,⁵⁹ prostate cancer,⁶⁰ head and neck squamous cell carcinoma,⁶¹ acute lymphocytic leukemia, lymphoma, and myeloma cell lines.⁶²

Topoisomerase inhibitors, like irinotecan and topotecan, are a type of chemotherapeutic agents that were derived from camptothecin from the bark of *Camptotheca acuminata* (Xishu, 喜樹). This TCM herb was found to reach level 2 of hepatotoxicity causality.

Causality Assessment

As demonstrated in the tables above, there are varying levels of evidence in the current literature. However, the clinical

Table 3. Single Herbs With Hepatotoxic Risks.

中藥名	Commonly Known as	Scientific Name	Level of Causality	No. of Case
雞骨草	Ji Gu Cao	<i>Abrus cantoniensis</i> ¹³⁻¹⁵	3	1
刺五加	Ci Wu Jia	<i>Acanthopanax senticosus</i> ¹⁴	3	1
刺五加	Ci Wu Jia	<i>Acanthopanax senticosus</i> ¹³⁻¹⁵	2	2
七日量	Qi Ri Yun, Chi R Yun	<i>Breynia officinalis</i> ^{13,14,24}	3	19
七日量	Qi Ri Yun, Chi R Yun	<i>Breynia officinalis</i> ^{14,15}	2	2
綠茶	Lu Cha/Green tea/Chaso	<i>Camellia sinensis</i> ^{13,14}	3	12
綠茶	Lu Cha/Green tea/Chaso	<i>Camellia sinensis</i> ¹⁴	2	121
綠茶	Lu Cha/Green tea/Chaso	<i>Camellia sinensis</i> ¹⁸	1	—
積雪草	Ji Xue Cao, Gotu kola	<i>Centella asiatica</i> ¹⁴	3	1
積雪草	Ji Xue Cao, Gotu kola	<i>Centella asiatica</i> ¹⁵	2	2
鯪魚膽	Carp gallbladder	<i>Ctenopharyngodon idella</i> ²⁵	3	1
白鮮皮	Bai Xian Pi	<i>Dictamnus dasycarpus</i> ¹⁶	3	32
白鮮皮	Bai Xian Pi	<i>Dictamnus dasycarpus</i> ^{14,15}	2	20
麻黃	Ma Huang	<i>Ephedra sinica</i> ¹⁴	3	1
麻黃	Ma Huang	<i>Ephedra sinica</i> ^{14,15}	2	6
麻黃	Ma Huang	<i>Ephedra species</i> ¹⁸	1	—
土三七	Tu San Qi	<i>Gynura segetum</i> /Radix <i>Gynurae Segeti</i> ¹⁴	3	2
土三七	Tu San Qi	<i>Gynura segetum</i> /Radix <i>Gynurae Segeti</i> ^{14,17,19}	2	171
枳椇子	Ji Ju Zi, Jiguja	<i>Hovenia dulcis</i> ¹⁴	3	1
枳椇子	Ji Ju Zi, Jiguja	<i>Hovenia dulcis</i> ¹⁴	2	1
金不換	Jin Bu Huan	<i>Lycopodium serratum</i> ¹⁴	3	1
金不換	Jin Bu Huan	<i>Lycopodium serratum</i> ^{14,15}	2	10
人參	Ren Shen, Ginseng	Intravenous Wild Ginseng Pharmacopuncture ¹⁶	3	1
人參	Ren Shen, Ginseng	<i>Panax ginseng</i> ¹³⁻¹⁵	2	6
何首烏	He Shou Wu, Hoshouwu	<i>Polygoni multiflori</i> / <i>Polygonum multiflorum</i> ^{9,16}	3	147
何首烏	He Shou Wu, Hoshouwu	<i>Polygoni multiflori</i> / <i>Polygonum multiflorum</i> ^{13,15,17,21}	2	516
何首烏	He Shou Wu, Hoshouwu	<i>Polygoni multiflori</i> / <i>Polygonum multiflorum</i> ^{9,19,21-23}	1	—
葉下珠	Ye XiaZhu	<i>Phyllanthus urinaria</i> ¹³⁻¹⁵	3	1
黃芩	Huang Qin	<i>Scutellaria baicalensis</i> ^{13,14}	3	1
黃芩	Huang Qin	<i>Scutellaria baicalensis</i> ¹³⁻¹⁵	2	22
血見愁	Xue Jian Chou	<i>Teucrium viscidum</i> ²⁶	3	1
翼枝榆	Yi Zhi Yu	<i>Ulmus davidiana</i> var <i>japonica</i> Nakai ¹⁶	3	3
附子	Fu Zi	<i>Aconitum carmichaeli</i> ¹⁷	2	13
當歸	Dang Gui	<i>Angelica sinensis</i> ^{13,15}	2	—
茵陳蒿	Yin Chen Hao	<i>Artemisia capillaris</i> ^{14,15}	2	7
柴胡	Chai Hu	<i>Bupleurum falcatum</i> ¹³⁻¹⁵	2	28
決明子	Jue Ming Zi	<i>Cassia obtusifolia</i> ^{15,17}	2	18
喜樹	Xi Shu	<i>Camptotheca acuminata</i> ¹³⁻¹⁵	2	—
及己	Ji Ji	<i>Chloranthus serratus</i> ¹³⁻¹⁵	2	—
珠果黃堇	Zh Guo Huang Jin, Hwang Geun Cho	<i>Corydalis speciosa</i> ¹⁵	2	—
延胡索	Yan Hu Suo	<i>Corydalis yanhusuo</i> ¹⁷	2	36
延胡索	Yan Hu Suo	<i>Corydalis yanhusuo</i> ¹⁸	1	—
瞿麥	Qu Mai	<i>Dianthus superbus</i> ²⁰	2	1
常山	Chang Shan	<i>Dichroa root</i> ²⁰	2	1
常山	Chang Shan	<i>Dichroa febrifuga</i> Lour ¹³	1	—
五倍子	Wu Bei Zi	<i>Galla chinensis</i> ¹³⁻¹⁵	2	—
毛果天芥菜	Mao Guo Tian Jie Cai	<i>Heliotropium lasiocarpum</i> ¹³⁻¹⁵	2	4
紫草科植物	—	<i>Heliotropium</i> ¹⁸	1	—

(continued)

Table 3. (continued)

中藥名	Commonly Known as	Scientific Name	Level of Causality	No. of Case
益母草	Yi Mu Cao	<i>Leonuri japonici</i> ²⁰	2	1
川楝子	Chuan Lian Zi	<i>Melia toosendan</i> fruit ^{15,20}	2	1
薄荷	Hu Bo He You	<i>Mentha pulegium</i> ¹³⁻¹⁵	2	—
石榴皮	Shi Liu Pi	<i>Pericarpium granati</i> ¹³⁻¹⁵	2	—
虎杖	Hu Zhang	<i>Polygonum cuspidatum</i> ¹³⁻¹⁵	2	—
破故紙	Po Gu Zhi, Bol Gol Zhee	<i>Psoralea corylifolia</i> ¹³⁻¹⁷	2	44
葛屬植物	Kudzu	<i>Pueraria thunbergiana</i> ¹³⁻¹⁵	2	6
大黃	Da Huang	<i>Rheum officinale/Rheum palmatum</i> ^{15,17}	2	24
丹蔘	Dan Shen	<i>Salvia miltiorrhiza</i> root ²⁰	2	1
天花粉	Tian Hua Fen	<i>Trichosanthes kirilowii</i> ¹³⁻¹⁵	2	—
合歡皮	He Huan Pi	<i>Albizia julibrissin</i> ¹³	1	—
艾葉	Ai Ye	<i>Artemisia argyi</i> ¹³	1	—
蒼朮	Cang Zhu Gan	<i>Atractylis gummifera</i> ¹⁸	1	—
小米辣	Xiao Mi La, Tobasco pepper	<i>Capsicum frutescens</i> ¹⁸	1	—
杜仲	Du Zhong	<i>Cortex eucommiae</i> ²⁷	1	—
豬屎豆	Zhu Shi Dou	<i>Crotalaria</i> ¹⁸	1	—
莪朮	E Zhu	<i>Curcuma phaeocaulis</i> ²⁷	1	—
黃藥子	Huang Yao Zi	<i>Dioscorea bulbifera</i> L ^{13,27}	1	—
八角蓮	Ba Jiao Lian	<i>Dysosma versipellis</i> ²⁷	1	—
吳茱萸	Wu Zhu Yu	<i>Evodia rutaecarpa</i> ²⁷	1	—
苦楝子	Ku Lian Zi	<i>Melia azedarach</i> ¹³	1	—
石花	Shi Hua	<i>Parmelia saxatilis</i> ¹⁸	1	—
商陸	Shang Lu	<i>Phytolacca acinosa</i> Roxb ¹³	1	—
苦參	Ku Shen	<i>Radix sophora</i> ²⁷	1	—
重樓皂莢	Chong Lou Zao Gan	<i>Rhizoma Paridis saponins</i> ³⁰	1	—
肉豆蔻	Rou Dou Kou	<i>Semen myristicae</i> ²⁷	1	—
千里光	Qian Li Guang	<i>Senecio scandens</i> ^{13,18,27}	1	—
番瀉葉	Fan Xie Ye	<i>Sennae folium</i> ²⁷	1	—
雷公藤	Lei Gong Teng	<i>Tripterygium wilfordii</i> ^{13,28,29}	1	—
蒼耳子	Cang Er Zi	<i>Xanthium sibiricum/Xanthium strumarium</i> L fruits ^{13,31}	1	—
生姜	Sheng Jiang	<i>Zingiber officinale</i> Roscoe ²⁷	1	—

and histopathological features of herb-induced liver toxicity may mimic any liver injury histopathological model,⁶³ and expert judgement could be limited by subjectivity. Hence, a widely accepted and standardized algorithm is needed to confirm causality. RUCAM is a quantitative scale that has been used worldwide,^{17,64-66} allowing results to be comparable across countries. When compared with other general causality assessment algorithms like the Naranjo scale, it is more liver-specific and more relevant.¹² Among liver-oriented methods, RUCAM was found to be superior. Clinical Diagnostic Scale showed poorer discriminative power, whereas the Digestive Disease Week-Japan scale included an in vitro drug lymphocyte stimulation test evaluation criterion, which was not widely accessible.⁶⁷ RUCAM also addresses other alternative causes of liver injury like concomitant drug use. Therefore, RUCAM is by far the most preferred algorithm used in the field.

Future Implications

First of all, we should note the presence of different types of evidence in the literature. Without following established causality algorithms, problems like comedication and poor data quality may affect the establishment of causality; hence, it is unjustifiable to ascertain the causal relationship immediately. Furthermore, contaminants during production and processing may lead to liver injury. Hence, clear-cut causality is often difficult to achieve. Our review presented the stratification of causality of the current literature. RUCAM is an important tool that should be applied to all future cases to determine causality accurately. Further studies are needed to confirm the causality of herb-induced liver injury with RUCAM in order to clarify the hepatotoxicity of herbs that are suspected in the literature. The use of RUCAM should be encouraged among physicians to aid diagnosis,

Table 4. Herb Concoctions With Hepatotoxic Risks.

中成藥/方劑	TCM Concoctions	Level of Causality	No. of Cases
丹鹿通督片: 丹參、鹿角膠、黃芪、延胡索、杜仲	Dan-lu-tong-du tablet: <i>Salvia miltiorrhiza</i> , <i>Cervi cornus Colla</i> , <i>Astragalus membranaceus</i> , <i>Corydalis yanhusuo</i> , <i>Eucommia ulmoides</i> ¹⁷	3	1
首烏片: 牛膝, 菟絲, 鱧腸, 女楨, 忍冬, 桑白皮, 何首烏, 補骨脂, 地黃, 金櫻子, 芝麻, 豨薟	Shou Wu Pian: <i>Achyranthes bidentata</i> , <i>Cuscuta chinensis</i> , <i>Eclipta prostrata</i> , <i>Ligustrum lucidum</i> , <i>Lonicera japonica</i> , <i>Morus alba</i> , <i>Polygonum multiflorum</i> , <i>Psoralea corylifolia</i> , <i>Rehmannia glutinosa</i> , <i>Rosa laevigata</i> , <i>Sesemum indicum</i> , <i>Siegesbeckia orientalis</i> ¹⁴	3	1
首烏片: 牛膝, 菟絲, 鱧腸, 女楨, 忍冬, 桑白皮, 何首烏, 補骨脂, 地黃, 金櫻子, 芝麻, 豨薟	Shou Wu Pian: <i>Achyranthes bidentata</i> , <i>Cuscuta chinensis</i> , <i>Eclipta prostrata</i> , <i>Ligustrum lucidum</i> , <i>Lonicera japonica</i> , <i>Morus alba</i> , <i>Polygonum multiflorum</i> , <i>Psoralea corylifolia</i> , <i>Rehmannia glutinosa</i> , <i>Rosa laevigata</i> , <i>Sesamum indicum</i> , <i>Siegesbeckia orientalis</i> ^{14,15}	2	17
防風通聖散: 黃芩, 滑石, 甘草, 石膏, 桔梗, 防風, 川芎, 當歸, 白芍, 大黃, 麻黃, 薄荷, 連翹, 芒硝, 荊芥, 白朮, 梔子	Bangpungtongsung-san: <i>Scutellariae Radix</i> , <i>Talcum</i> , <i>Glycyrrhiza uralensis</i> Fischer, <i>gypsum</i> , <i>Platycodonis Radix</i> , <i>Saposhnikoviae Radix</i> , <i>Cnidii Rhizoma</i> , <i>Angelicae Gigantis Radix</i> , <i>Paeoniae Radix</i> , <i>Rhei Rhizoma</i> , <i>Ephedrae Herba</i> , <i>Menthae Herba</i> , <i>Forsythia suspensa</i> Vahl, <i>Natrii Sulfas</i> , <i>Schizonepetae Spica</i> , <i>Atractylodes macrocephala</i> Koidzumi, <i>Gardeniae Fructus</i> ¹⁶	3	1
漢方防風通聖散: 當歸, 蒼朮, 蛇床子, 梔子, 麻黃, 連翹, 甘草, 石膏, 防風, 薄荷, 牡丹, 桔梗, 大黃, 荊芥, 黃芩和姜, 滑石粉和硫酸鈉。	Bofu Tsu Sho San: <i>Angelica</i> , <i>Atractylis</i> , <i>Cnidium</i> , <i>Gardenia</i> , <i>Ephedra</i> , <i>Forsythia</i> , <i>Glycyrrhiza</i> , <i>Gypsum fibrosum</i> , <i>Ledebouriella</i> , <i>Mentha</i> , <i>Paeonia</i> , <i>Platycodon</i> , <i>Rheum</i> , <i>Schizonepeta</i> , <i>Scutellaria</i> and <i>Zingiber</i> ; <i>Kadinum</i> (talcum powder), and <i>sodium sulfuricum</i> ¹³⁻¹⁵	2	1
加味五積散: 蒼朮, 陳皮, 厚朴, 桔梗, 枳殼, 當歸, 茯苓, 半夏, 川芎, 白芷, 肉桂, 桃仁, 紅花, 秦艽, 五加皮, 甘草, 生薑, 東亞鉗蠍, 蜈蚣, 馬錢子, 白屈菜, 延胡索, 黃芩, 黃連, 蘆根, 草烏	Gamiojuck-san: <i>Atractylodis Rhizoma</i> , <i>Citrus unshiu</i> Markovich, <i>Magnolia officinalis</i> , <i>Platycodonis Radix</i> , <i>Aurantii Fructus Immaturus</i> , <i>Zingiber officinale</i> , <i>Angelicae Gigantis Radix</i> , <i>Poria Sclerotium</i> , <i>Pinellia ternata</i> Breitenbach, <i>Cnidium officinale</i> Makino, <i>Angelicae Dahuricae Radix</i> , <i>Cinnamomi Ramulus</i> , <i>Persicae Semen</i> , <i>Carthami Flos</i> , <i>Gentianae Macrophyllae Radix</i> , <i>Acanth opanacis Cortex</i> , <i>Glycyrrhiza uralensis</i> Fischer, <i>Zingiber officinale</i> , <i>Buthus martensii</i> Karsch, <i>Scolopendra</i> , <i>Strychni Semen</i> , <i>Chelidonii Herba</i> , <i>Corydalis Tuber</i> , <i>Scutellariae Radix</i> , <i>Coptidis Rhizoma</i> , <i>Phragmitis Rhizoma</i> , <i>Aconiti Kusnezoffii Tuber</i> ¹⁶	3	1
加味六君子湯: 香附, 生姜, 大棗, 白朮, 茯苓, 陳皮, 半夏, 人參根, 紫蘇葉, 土木香, 砂仁	Gamiyukgunja-tang: <i>Cyperis Rhizoma</i> , <i>Zingiber officinale</i> , <i>Zizyphi Fructus</i> , <i>Atractylodes macrocephala</i> Koidzumi, <i>Poria Sclerotium</i> , <i>Citrus unshiu</i> Markovich, <i>Pinellia ternata</i> Breitenbach, <i>Ginseng Radix</i> , <i>Perillae Folium</i> , <i>Inula helenium</i> , <i>Amomi Fructus</i> ¹⁶	3	1
附子草烏加減方: 附子, 草烏	Herbal Medicine including Boo-ja and Cheon-o: <i>Aconiti Lateralis Radix Preparata</i> , <i>Aconiti Kusnezoffii Tuber</i> were indicated and others were unknown ¹⁶	3	1
黃蓮加減方: 黃蓮	Herbal Medicine Including <i>Coptidis Rhizoma</i> : only <i>Coptidis Rhizoma</i> was indicated in original article; others were unknown ¹⁶	3	1

(continued)

Table 4. (continued)

中成藥/方劑	TCM Concoctions	Level of Causality	No. of Cases
白鮮加減方：白鮮，葛根，升麻，蒺藜，浮萍，麥冬，地黃，甘草	Herbal medicine including <i>Dyctamnus dasycarpus</i> : <i>Dictamnus dasycarpus</i> , <i>Pueraria thunbergiana</i> Bentham, <i>Cimicifuga heracleifolia</i> , <i>Tribulus terrestris</i> L, <i>Spirodela</i> Herba, <i>Liriopsis</i> seu <i>Ophiopogonis Tuber</i> , <i>Rehmanniae Radix Preparata</i> , <i>Glycyrrhiza uralensis</i> Fischer ¹⁶	3	1
少陽人獨活地黃湯：山茱萸，茯苓，澤瀉，牡丹皮，防風，東北土當歸（+石膏）	Soyangin Dokwhaljiwhang-tang: <i>Rehmanniae Radix Preparata</i> , <i>Cornus officinalis</i> , <i>Poria Sclerotium</i> , <i>Alismatis Rhizoma</i> , <i>Moutan Radicis Cortex</i> , <i>Saposhnikoviae Radix</i> , <i>Araliae Continentalis Radix (+gypsum)</i> ¹⁶	3	1
六味地黃元：澤瀉，地黃，山茱萸，山藥，麥冬，澤瀉，牡丹皮，茯苓	Yugmijihwang-won: <i>Alismatis Rhizomaa</i> , <i>Rehmanniae Radix Preparata</i> , <i>Cornus officinalis</i> , <i>Dioscoreae Rhizoma</i> , <i>Alismatis Rhizoma</i> , <i>Moutan Radicis Cortex</i> , <i>Poria Sclerotium</i> ¹⁶	3	1
大柴胡湯：柴胡，人參，甘草，半夏，黃芩，薑和棗樹	Da Chai Hu Tang: <i>Bupleurum falcatum</i> , <i>Ginseng</i> , <i>Glycyrrhiza glabra</i> , <i>Pinellia</i> , <i>Scutellaria</i> , <i>Zingiber officinale</i> , and <i>Zizyphus jujuba</i> ¹³⁻¹⁵	2	1
複方青黛丸：白芷，板藍根，神曲，丹參，土茯苓	Fufangqingdaiyuan: <i>Angelica dahurica</i> , <i>Isatis indigotica</i> (Indigo naturalis), <i>Massa medicata fermentata</i> (yeast), <i>Salvia miltiorrhiza</i> , <i>Smilax glabra</i> ^{13,14}	2	1
漢方加味逍遙散：當歸，白朮，柴胡，梔子，甘草，薄荷，牡丹皮，白芍，茵陳和姜	Kamishoyosan: <i>Angelica sinensis</i> , <i>Atractylodes racea</i> , <i>Bupleurum falcatum</i> , <i>Gardenia</i> , <i>Glycyrrhiza glabra</i> , <i>Mentha haplocalyx</i> , <i>Moutan</i> , <i>Paeonia alba</i> , <i>Sclerotium Poriae Cocos</i> , and <i>Zingiber officinale</i> ¹³⁻¹⁵	2	1
龍丹瀉肝湯：木通，澤瀉，當歸，柴胡，梔子，龍膽，甘草，車前子，熟地黃和黃芩	Long Dan Xie Gan Tang: <i>Acebia</i> , <i>Alisma</i> , <i>Angelica sinensis</i> , <i>Bupleurum</i> , <i>Gardenia</i> , <i>Gentiana</i> , <i>Glycyrrhiza</i> , <i>Plantago</i> , <i>Rehmannia</i> , and <i>Scutellaria</i> ¹³⁻¹⁵	2	17
小柴胡湯：柴胡，人參，甘草，半夏，黃芩，薑和大棗	Syosaikoto/Xiao Chai Hu Tang: <i>Bupleurum falcatum</i> , <i>Ginseng</i> , <i>Glycyrrhiza glabra</i> , <i>Pinellia tuber</i> , <i>Scutellaria baicalensis</i> , <i>Zingiber officinale</i> , <i>Zizyphus jujuba</i> ^{14,15}	2	20
小柴胡湯：柴胡，人參，甘草，半夏，黃芩，薑和大棗	Syosaikoto/Xiao Chai Hu Tang: <i>Bupleurum falcatum</i> , <i>Ginseng</i> , <i>Glycyrrhiza glabra</i> , <i>Pinellia tuber</i> , <i>Scutellaria baicalensis</i> , <i>Zingiber officinale</i> , <i>Zizyphus jujuba</i> ²³	1	—
桃紅四物湯：桃仁，紅花，熟幹地黃，當歸，赤芍，川芎	Tao-hong-si-wu decoction: <i>Semen Persicae</i> , <i>Flos Carthami</i> , <i>Radix Rehmanniae</i> , <i>Radix Angelicae Sinensis</i> , <i>Radix Paeoniae Rubra</i> , <i>Rhizoma Chuanxiong</i> ³²	1	—

and RUCAM should be employed before publication of cases and inclusion in databases.

In Chinese communities, there is a common misconception that TCM is free of side effects and toxicities. Our review highlights the importance to evaluate the potential hepatotoxicity of TCM. We suggest that there is a fundamental need for raising the awareness of this issue among Chinese communities. Cancer patients should consult TCM practitioners before using TCM, instead of taking TCM without professional advice.

Also, TCM can have hepatoprotective effects. However, proving the hepatoprotective effects of a herb clinically can be challenging, and the therapeutic benefit of TCM is often

questioned. TCM herbs are rarely used alone, as each patient receives a personally tailored concoction. Hence, the effectiveness of TCM is difficult to be proven in the Western-dominated setting based on a medical system that treats the same disease with the same drug on different patients.

In practice, oncologists are often uncertain of the efficacy and safety of TCM and therefore urge patients not to take any TCM during systemic treatment. TCM has been practiced for over 2000 years, and its ideologies and effectiveness have been deeply rooted and accepted in Chinese communities. A survey done in Hong Kong found that over two thirds of all interviewed Chinese cancer patients

Table 5. TCM Herbs Found to Have Hepatotoxic Properties in the Laboratory Setting.

中草藥/成藥/方劑	TCM Herb or Concoction
刺五加	<i>Acatopanax senticosus</i> (Rupr et Maxim) Harms ³³
紅豆	Adzuki bean (<i>Phaseolus aureus</i> Roxb) ³⁴
蛇葡萄	<i>Ampelopsis brevipedunculata</i> (Maxim) Trautv (Vitaceae) ³⁵
牛樟芝	<i>Antrodia camphorata</i> ^{36,37}
黃花蒿	<i>Artemisia annua</i> L ³⁸
赤小豆	Black bean (<i>Glycine max</i> [L] Merr) ³⁴
綠豆	Mung bean (<i>Phaseolus radiatus</i> L) ³⁴
三七	<i>Panax notoginseng</i> ²⁹
白芍	Radix Paeoniae Alba ³⁹
赤芍	Radix Paeoniae Rubra ³⁹
地黃	<i>Rehmannia glutinosa</i> ²⁹
黑豆	Rice bean (<i>Phaseolus calcaratus</i> Roxb) ³⁴
丹參	<i>Salvia miltiorhiza</i> ⁴⁰
五味子	<i>Schisandra chinensis</i> ⁴¹
蒼耳	<i>Xanthium strumarium</i> ⁴²
二至丸: 女貞子 旱蓮草	Er-Zhi-Wan: Fructus Ligustri Lucidi, Herba Ecliptae ⁴³
桂枝茯苓丸: 桂枝 茯苓 桃仁 芍藥 牡丹皮	Guizhi-Fuling-Wan: Bark of <i>Cinnamomum cassia</i> Presl, Carpophores of <i>Poria cocos</i> Wolf, Seed of <i>Prunus persica</i> Batsch, Root of <i>Paeonia lactiflora</i> Pall, Root bark of <i>Paeonia suffruticosa</i> ⁴⁴
瀉青丸: 龍膽草 當歸 川芎 梔子 大黃 羌活 防風	Shieh-Qing-Wan: Root of <i>Angelica sinensis</i> Diels (Umbelliferae) Root and rhizome of <i>Gentiana scabra</i> Bunge (Gentianaceae) Fruit of <i>Gardenia jasminoides</i> Ellis (Rubiaceae) Root and rhizome of <i>Rheum palmatum</i> L (Polygonaceae) Rhizome of <i>Ligusticum chuanxiong</i> Hort. (Umbelliferae) Root and rhizome of <i>Notopterygium incisum</i> Ting (Umbelliferae) Root of <i>Saposhnikovia divaricata</i> Schischk (Umbelliferae) ⁴⁴
四逆散: 柴胡 · 白芍 · 枳實 · 甘草	Si Ni San: Radix bupleuri, Radix Paeoniae Alba, Fructus Aurantii Immaturus, Radix Glycyrrhizae ⁴⁵
四磨飲: 人參 · 檳榔 · 沉香 · 烏藥	Syh-Mo-Yiin: Root of <i>Panax ginseng</i> CA Meyer (Araliaceae) Seed of <i>Areca catechu</i> L (Palmae) Lignum of <i>i</i> Roxb. (Euphorbiaceae) Root of <i>Lindera strychn</i> (<i>li-lia</i> Vill (Lauraceae) ⁴⁴
茵陳蒿湯: 茵陳, 梔子, 大黃	Yin Chen Hao Tang: <i>Artemisia capillaris</i> Thunb (Tarragon), <i>Gardenia jasminoides</i> Ellis (Gardenia), and <i>Rheum officinale</i> Baill (Rhubarb) ⁴⁶

Abbreviation: TCM, traditional Chinese medicine.

believed that integrated TCM and Western medicine was effective in treating cancer.⁷ Hence, Chinese cancer patients are keen to use TCM. The total rejection by some oncologists may prompt patients to hide the truth. The aforementioned survey found that among patients who were concurrently receiving Western medicine treatment and TCM, nearly two thirds of them did not inform their physicians. This is not only harmful to the doctor-patient relationship but also unhelpful in monitoring and treating the patient.

Recent research has shown that certain TCM when used in combination with Western medicine can be beneficial. It was found that some TCM could act as effective chemosensitizers and radiosensitizers, and could be helpful in palliative care.⁶⁸ We have learnt from history that some modern anticancer drugs were derived from plants. The Pacific Yew, the Madagascar Periwinkle, and the Chinese happy tree have yielded valuable chemicals for chemotherapy. If

TCM was excluded from treating cancer patients, the advancement of cancer therapy may be hindered. More research is needed to clarify the hepatotoxicity and hepatoprotectiveness of different TCM herbs and concoctions. This is crucial to aid TCM practitioners and Western medicine doctors in making clinical decisions, as well as paving the way for TCM and Western medicine integration in treating cancer.

Conclusion

This literature review compiled a list of hepatotoxic and hepatoprotective TCM herbs and concoctions, and highlighted some that are highly likely to be used by cancer patients as they either have anticancer properties or symptom relief purposes. They were then stratified according to their levels of causality, to provide a clearer and more clinically relevant picture of the current evidence. More

stringent research with the use of RUCAM is needed to confirm the causality of herb-induced liver injury before publication and inclusion in databases. Cancer patients should note the potential hepatotoxic effects of TCM herbs and should not assume the absence of side effects of TCM herbs. More collaboration between TCM and Western medicine should be encouraged to establish effective and safe screening of drug-herb interaction.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Hei Ching Chow  <https://orcid.org/0000-0002-0825-9637>

References

- Xu W, Towers A, Li P, Collet JP. Traditional Chinese medicine in cancer care: perspectives and experiences of patients and professionals in China. *Eur J Cancer Care (Engl)*. 2006;15:397-403.
- Wong R, Sagar C, Sagar S. Integration of Chinese medicine into supportive cancer care: a modern role for an ancient tradition. *Cancer Treat Rev*. 2001;27:235-246.
- Simpson PB. Family beliefs about diet and traditional Chinese medicine for Hong Kong women with breast cancer. *Oncol Nurs Forum*. 2003;30:834-840.
- Chen Z, Gu K, Zheng Y, Zheng W, Lu W, Shu XO. The use of complementary and alternative medicine among Chinese women with breast cancer. *J Altern Complement Med*. 2008;14:1049-1055.
- Chui YY, Donoghue J, Chenoweth L. Responses to advanced cancer: Chinese-Australians. *J Adv Nurs*. 2005;52:498-507.
- Chan HY, Chui YY, Chan CW, et al. Exploring the influence of traditional Chinese medicine on self-care among Chinese cancer patients. *Eur J Oncol Nurs*. 2014;18:445-451.
- Lam YC, Cheng CW, Peng H, Law CK, Huang X, Bian Z. Cancer patients' attitudes towards Chinese medicine: a Hong Kong survey. *Chin Med*. 2009;4:25.
- Yufang H. Chinese medicine is mild and does not hurt the body? The concept is wrong [in Chinese]. *Joint Evening News*. <https://health.udn.com/health/story/6035/360612>. Published September 23, 2014. Accessed July 31, 2017.
- Wang J, Ma Z, Niu M, et al. Evidence chain-based causality identification in herb-induced liver injury: exemplification of a well-known liver-restorative herb *Polygonum multiflorum*. *Front Med*. 2015;9:457-467.
- Ting A, Chow Y, Tan W. Microbial and heavy metal contamination in commonly consumed traditional Chinese herbal medicines. *J Tradit Chin Med*. 2013;33:119-124.
- Tillmann HL, Suzuki A, Barnhart HX, Serrano J, Rockey DC. Tools for causality assessment in drug-induced liver disease. *Curr Opin Gastroenterol*. 2019;35:183-190.
- Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci*. 2015;17:E14.
- Frenzel C, Teschke R. Herbal hepatotoxicity: clinical characteristics and listing compilation. *Int J Mol Sci*. 2016;17:E588.
- Teschke R, Zhang L, Long H, et al. Traditional Chinese medicine and herbal hepatotoxicity: a tabular compilation of reported cases. *Ann Hepatol*. 2015;14:7-19.
- Teschke R, Wolff A, Frenzel C, Schulze J. Review article: herbal hepatotoxicity—an update on traditional Chinese medicine preparations. *Aliment Pharmacol Ther*. 2014;40:32-50.
- Lee WJ, Kim HW, Lee HY, Son CG. Systematic review on herb-induced liver injury in Korea. *Food Chem Toxicol*. 2015;84:47-54.
- Zhu Y, Niu M, Chen J, et al. Hepatobiliary and pancreatic: comparison between Chinese herbal medicine and Western medicine-induced liver injury of 1985 patients. *J Gastroenterol Hepatol*. 2016;31:1476-1482.
- Huang SH, Tung CW, Fülöp F, Li JH. Developing a QSAR model for hepatotoxicity screening of the active compounds in traditional Chinese medicines. *Food Chem Toxicol*. 2015;78:71-77.
- Wang JB, Zhu Y, Bai ZF, Wang FS, Li XH, Xiao XH; Branch Committee of Hepatobiliary Diseases and Branch Committee of Chinese Patent Medicines, China Association of Chinese Medicine. Guidelines for the diagnosis and management of herb-induced liver injury. *Chin J Integr Med*. 2018;24:696-706.
- Critchley LA, Chen DQ, Chu TT, Fok BS, Yeung C. Pre-operative hepatitis in a woman treated with Chinese medicines. *Anaesthesia*. 2003;58:1096-1100.
- Li C, Niu M, Bai Z, et al. Screening for main components associated with the idiosyncratic hepatotoxicity of a tonic herb, *Polygonum multiflorum*. *Front Med*. 2017;11:253-265.
- Ruan LY, Li MH, Xing YX, et al. Hepatotoxicity and hepatoprotection of *Polygonum multiflorum* Thund as two sides of the same biological coin. *J Ethnopharmacol*. 2019;230:81-94.
- Hong M, Li S, Tan HY, et al. A network-based pharmacology study of the herb-induced liver injury potential of traditional hepatoprotective Chinese herbal medicines. *Molecules*. 2017;22:E632.
- Lin TJ, Su CC, Lan CK, Jiang DD, Tsai JL, Tsai MS. Acute poisonings with *Breynia officinalis*—an outbreak of hepatotoxicity. *J Toxicol Clin Toxicol*. 2003;41:591-594.
- Kung SW, Chan YC, Tse ML, Lau FL, Chau TL, Tam MK. Acute renal failure and hepatitis following ingestion of carp gallbladder. *Clin Toxicol (Phila)*. 2008;46:753-757.
- Poon WT, Chau TL, Lai CK, et al. Hepatitis induced by *Teucrium viscidum*. *Clin Toxicol (Phila)*. 2008;46:819-822.
- Zhao P, Liu B, Wang C. Hepatotoxicity evaluation of traditional Chinese medicines using a computational molecular model. *Clin Toxicol (Phila)*. 2017;55:996-1000.
- Qu L, Qu F, Jia Z, Wang C, Wu C, Zhang J. Integrated targeted sphingolipidomics and transcriptomics reveal abnormal sphingolipid metabolism as a novel mechanism of the hepatotoxicity and nephrotoxicity of triptolide. *J Ethnopharmacol*. 2015;170:28-38.

29. Zhang Q, Li Y, Liu M, Duan J, Zhou X, Zhu H. Compatibility with *Panax notoginseng* and *Rehmannia glutinosa* alleviates the hepatotoxicity and nephrotoxicity of *Tripterygium wilfordii* via modulating the pharmacokinetics of triptolide. *Int J Mol Sci*. 2018;19:E305.
30. Man S, Qiu P, Li J, Zhang L, Gao W. Global metabolic profiling for the study of *Rhizoma Paridis* saponins-induced hepatotoxicity in rats. *Environ Toxicol*. 2017;32:99-108.
31. Xue LM, Zhang QY, Han P, et al. Hepatotoxic constituents and toxicological mechanism of *Xanthium strumarium* L fruits. *J Ethnopharmacol*. 2014;152:272-282.
32. Xi S, Shi M, Jiang X, et al. The effects of Tao-Hong-Si-Wu on hepatic necroinflammatory activity and fibrosis in a murine model of chronic liver disease. *J Ethnopharmacol*. 2016;180:28-36.
33. Lin CC, Huang PC. Antioxidant and hepatoprotective effects of *Acatopanax senticosus*. *Phytother Res*. 2000;14:489-494.
34. Wu SJ, Wang JS, Lin CC, Chang CH. Evaluation of hepatoprotective activity of legumes. *Phytomedicine*. 2001;8:213-219.
35. Yabe N, Matsui H. *Ampelopsis brevipedunculata* (Vitaceae) extract inhibits a progression of carbon tetrachloride-induced hepatic injury in the mice. *Phytomedicine*. 2000;7:493-498.
36. Hsiao G, Shen MY, Lin KH, et al. Antioxidative and hepatoprotective effects of *Antrodia camphorata* extract. *J Agric Food Chem*. 2003;51:3302-3308.
37. Shih YL, Wu MF, Lee CH, et al. *Antrodia cinnamomea* reduces carbon tetrachloride-induced hepatotoxicity in male Wistar rats. *In Vivo*. 2017;31:877-884.
38. Sun H, Zhang AH, Zou DX, Sun WJ, Wu XH, Wang XJ. Metabolomics coupled with pattern recognition and pathway analysis on potential biomarkers in liver injury and hepatoprotective effects of yinchenhao. *Appl Biochem Biotechnol*. 2014;173:857-869.
39. Wang R, Xiong AZ, Teng ZQ, Yang QW, Shi YH, Yang L. Radix Paeoniae Rubra and Radix Paeoniae Alba attenuate CCl₄-induced acute liver injury: an ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) based metabolomic approach for the pharmacodynamic study of traditional Chinese medicines (TCMs). *Int J Mol Sci*. 2012;13:14634-14647.
40. Hase K, Kasimu R, Basnet P, Kadota S, Namba T. Preventive effect of lithospermate B from *Salvia miltiorrhiza* on experimental hepatitis induced by carbon tetrachloride or D-galactosamine/lipopolysaccharide. *Planta Med*. 1997;63:22-26.
41. Zhu M, Lin KF, Yeung RY, Li RC. Evaluation of the protective effects of *Schisandra chinensis* on phase I drug metabolism using a CCl₄ intoxication model. *J Ethnopharmacol*. 1999;67:61-68.
42. Hossen MJ, Kim MY, Cho JY. MAPK/AP-1-targeted anti-inflammatory activities of *Xanthium strumarium*. *Am J Chin Med*. 2016;44:1111-1125.
43. Yao W, Gu H, Zhu J, et al. Integrated plasma and urine metabolomics coupled with HPLC/QTOF-MS and chemometric analysis on potential biomarkers in liver injury and hepatoprotective effects of Er-Zhi-Wan. *Anal Bioanal Chem*. 2014;406:7367-7378.
44. Tsai CC, Kao CT, Hsu CT, Lin CC, Lin JG. Evaluation of four prescriptions of traditional Chinese medicine: syh-mo-yiin, guizhi-fuling-wan, shieh-qing-wan and syh-nih-sann on experimental acute liver damage in rats. *J Ethnopharmacol*. 1997;55:213-222.
45. Jiang J, Zhou C, Xu Q. Alleviating effects of si-ni-san, a traditional Chinese prescription, on experimental liver injury and its mechanisms. *Biol Pharm Bull*. 2003;26:1089-1094.
46. Yang Q, Yang F, Tang X, et al. Chlorpromazine-induced perturbations of bile acids and free fatty acids in cholestatic liver injury prevented by the Chinese herbal compound Yin-Chen-Hao-Tang. *BMC Complement Altern Med*. 2015;15:122.
47. Decai TXJ. *Science of Chinese Materia Medica*. Shanghai, China: Shanghai College of Traditional Chinese Medicine; 2003.
48. Xu X, You K. *English-Chinese Encyclopedia of Practical Traditional Chinese Medicine*. Beijing, China: Higher Education Press; 1990.
49. Hong Kong Baptist University School of Chinese Medicine. Chinese Medicinal Material Images Database. <http://libproj.ct.hkbu.edu.hk/was40/search?lang=eng&channelid=47953>. Accessed July 31, 2019.
50. Baeg IH, So SH. The world ginseng market and the ginseng (Korea). *J Ginseng Res*. 2013;37:1-7.
51. Lin G, Wang JY, Li N, et al. Hepatic sinusoidal obstruction syndrome associated with consumption of *Gynura segetum*. *J Hepatol*. 2011;54:666-673.
52. Guo XX, Zhao LN, Wang J, et al. Chemical constituents from root barks of *Dictamnus dasycarpus* and their cytotoxic activities [in Chinese]. *Zhongguo Zhong Yao Za Zhi*. 2018;43:4869-4877.
53. Chen H, Li S, Wang S, Li W, Bao N, Ai W. The inhibitory effect of kokusaginine on the growth of human breast cancer cells and MDR-resistant cells is mediated by the inhibition of tubulin assembly. *Bioorg Med Chem Lett*. 2018;28:2490-2492.
54. Thitimita S, Pithayanukul P, Nithitanakool S, Bavovada R, Leanpolchareanchai J, Saparpakorn P. *Camellia sinensis* L extract and its potential beneficial effects in antioxidant, anti-inflammatory, anti-hepatotoxic, and anti-tyrosinase activities. *Molecules*. 2017;22:E401.
55. Rafieian-Kopaei M, Movahedi M. Breast cancer chemopreventive and chemotherapeutic effects of *Camellia sinensis* (green tea): an updated review. *Electron Physician*. 2017;9:3838-3844.
56. Jia LY, Wu XJ, Gao Y, et al. Inhibitory Effects of total triterpenoid saponins isolated from the seeds of the tea plant (*Camellia sinensis*) on human ovarian cancer cells. *Molecules*. 2017;22:E1649.
57. Esghaei M, Ghaffari H, Esboei BR, Tapeh ZE, Salim FB, Motevalian M. Evaluation of anticancer activity of *Camellia sinensis* in the Caco-2 colorectal cancer cell line. *Asian Pac J Cancer Prev*. 2018;19:1697-1701.
58. Hong Kong Chinese Medicine Division Department of Health. Reference materials for Chinese herbal medicines related to adverse events in Hong Kong [in Chinese]. http://www.cmd.gov.hk/html/b5/health_info/publication/pdf/AdverseEvents_tc_bw.pdf. Accessed July 31, 2019.

59. Scheck AC, Perry K, Hank NC, Clark WD. Anticancer activity of extracts derived from the mature roots of *Scutellaria baicalensis* on human malignant brain tumor cells. *BMC Complement Altern Med*. 2006;6:27.
60. Ye F, Jiang S, Volshonok H, Wu J, Zhang DY. Molecular mechanism of anti-prostate cancer activity of *Scutellaria baicalensis* extract. *Nutr Cancer*. 2007;57:100-110.
61. Zhang DY, Wu J, Ye F, et al. Inhibition of cancer cell proliferation and prostaglandin E2 synthesis by *Scutellaria baicalensis*. *Cancer Res*. 2003;63:4037-4043.
62. Kumagai T, Müller CI, Desmond JC, Imai Y, Heber D, Koeffler HP. *Scutellaria baicalensis*, a herbal medicine: anti-proliferative and apoptotic activity against acute lymphocytic leukemia, lymphoma and myeloma cell lines. *Leuk Res*. 2007;31:523-530.
63. Suzuki A, Brunt EM, Kleiner DE, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. *Hepatology*. 2011;54:931-939.
64. Rathi C, Pipaliya N, Patel R, Ingle M, Phadke A, Sawant P. Drug induced liver injury at a tertiary hospital in India: etiology, clinical features and predictors of mortality. *Ann Hepatol*. 2017;16:442-450.
65. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology*. 2013;144:1419-1425,1425.e1-e3.
66. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005;129:512-521.
67. García-Cortés M, Stephens C, Lucena MI, Fernández-Castañer A, Andrade RJ. Causality assessment methods in drug induced liver injury: strengths and weaknesses. *J Hepatol*. 2011;55:683-691.
68. The Lancet Oncology. Rethinking traditional Chinese medicines for cancer. *Lancet Oncol*. 2015;16:1439.