Herb induced liver injury after using herbal medicine

A systemic review and case-control study

Nai-Hui Lin, MD, Hsiu-Wu Yang, MD, MS, Yu-Jang Su, MD, MS, Chen-Wang Chang, MD, MS

Abstract

In Taiwan, traditional herbal medication was included in Taiwan’s National Health Insurance (NHI) system since 1996 and in 9 out of 10 hospitals have developed their own departments of traditional medicine. This study aims to address the herb-induced liver injury (HILI) after using herbal medicine on the relationship between age, gender, epidemiology, laboratory data, pathogenesis, mobility, and mortality.

We searched the PubMed database with “hepatitis after herbal medicine” and “in human” till 2018 April and returned 163 articles in a systemic review manner. Two cases reports describing in-vitro liver injury were excluded. Reviews and articles without the detailed report, laboratory data and history were excluded from this study. In the end, there were 53 articles enrolled in this study. These enrolled literatures are from France (n = 13), Germany (n = 12), Switzerland (n = 5) United States of America (n = 4), Korea (n = 4), Hong Kong (n = 4), Greece (n = 3), China (n = 2), Canada (n = 1), Italy (n = 1), Thailand (n = 1), Finland (n = 1), Taiwan (n = 1), and Japan (n = 1). The data were analyzed with a commercial statistical software Stata/SE 12.0 program Stata Corporation, College Station, TX, USA. Statistical χ² tests were performed and the significance was set at a P value of less than .05 (2-tailed).

The ages are ranged from 15 to 78 years with the mean ± SD (standard deviation) of 48.3 ± 16.2 years old. The majority of cases are female (n = 37). In elderly, man is more commonly seen than female in HILI (37.5% vs 10.5%, P = .02). Female is vulnerable to cholestatic type of HILI than male (21.1% vs 0.0%, P = .04). Of all the cases in HILI, using pure substance are more commonly seen than mixed substance (P = .02). In gender, male patients have higher alanine aminotransferase (GPT) (ULN) level in HILI than female ones (1560 ± 819 vs 1047 ± 706, P = .03).

In HILI, the female is more commonly seen than male, but less than male in the elderly. The pure substance more often happens to HILI than mixture substance. Female is predominant in the cholestatic type of HILI. The major prevalence of HILI is in Europe rather than Asia. HILI cases in Europe is 2.75-fold than in Asia. This could be due to fewer reports of the herb induced liver injury in Asia compared to Europe. Prevention of HILI is the best policy, because it needs to take 78 ± 59 days to recover.

Abbreviations: ALP = alkaline phosphatase, CAM = complementary and alternative medicines, CIOMS = council for international organizations of medical sciences, DILI = drug-induced liver injury, DSHEA = dietary supplement health and education act, GPT = alanine aminotransferase, GWA = genome-wide association, HDS = herbal and dietary supplements, HILI = herb-induced liver injury, HLA = human leukocyte antigen, NDGA = nordihydroguaiaretic acid, RUCAM = Roussel Uclaf Causality Assessment Method, TAM = traditional oriental medicine, TCM = traditional herbal medication, TNF = tumor necrosis factor, TOM = traditional oriental medicine, ULN = upper limits of normal ranges.

Keywords: herb induced liver injury, herbal and dietary supplements (HDS), herbal medicine

1. Introduction

People promote their health and make herbal and dietary supplements (HDS) become more and more popular around the world nowadays. People taking HDS is thought to believe that it is more safe, effective and without any complication for their long-term health.1 However, Navarro et al had reported several cases of hepatotoxicity after usage of HDS.2 In Taiwan, traditional herbal medication (TCM) was included in Taiwan’s National Health Insurance (NHI) system since 1996 and in 9 out of 10 hospitals have developed their own departments of traditional medicine.3 Teschke et al had described a review of TCM causing liver Injury implying herbs may contain extensive venomous molecules, accumulation of hazardous components through the intestinal process and hepatic systems in 2014.4 It is very difficult for clinical physicians in identifying and early diagnosing the patients with herb-induced liver injury (HILI) by history taking and physical examination.5 Besides, patients seldom informed the family physicians of using these herbs...
because they can easily get herbs or complementary medications everywhere without doctor’s approved or prescriptions.\cite{6}

HILI presents in variable unspecific signs and symptoms with general weakness, gastrointestinal (GI) symptoms (i.e., abdomen distension, abdomen pain or fullness), or typical hepatitis symptoms. Presentations are very similar to drug-induced liver injury (DILI) or at least share the same pictures of liver injury which makes the differential diagnosis more difficult.\cite{5} There are many causality assessments helpful to highlight the possibility of HILI. Teschke et al claimed council for international organizations of medical sciences (CIOMS) scale is liver-specific, quantitative for liver and validated for hepatotoxicity but not suitable for non-hepatic adverse drug reactions (ADRs). In current causality assessment methods, only Naranjo scale is validated for non-hepatic ADRs.\cite{7}

Most herbal-induced hepatotoxicity cannot reproduce in experimental animal models. Thus, it is difficult to understand the pathogenetic factors.\cite{5} Current medical technology still cannot provide a highly specific and high sensitivity marker or standardized measurements to make a definite diagnosis of HILI. Clinical physicians can only make the diagnosis of HILI by exclusion. De Boer et al stated diagnosis of some hepatotoxicities cannot provide a highly specific and high sensitivity marker or standardized measurements to make a definite diagnosis of HILI. Clinical physicians can only make the diagnosis of HILI by exclusion. De Boer et al. stated diagnosis of some hepatotoxicities after specific herbal are made according to the typical clinical presentations.\cite{5,6} This study aims to address the hepatitis after using herbal medicine (HILI) on the relationship between age, gender, in herbal toxicity, the typical clinical pictures, epidemiology, laboratory data, pathogenesis, mobility, and mortality.

2. Materials and methods

A systemic review was designed to investigate the etiology, epidemiology, mechanism, recovery days of liver injury after using herbal medicine. A search of “hepatitis after herbal medicine” and “in human” till 2018 April from the PubMed database returned a total of 163 articles. Excluding the cases, reports of liver injury were in vitro. Reviews and articles without detailed report, laboratory data and history were excluded from this study. In the end, there were 53 articles enrolled in this study. The process of enrollment is shown in Figure 1. The combined data and descriptions of herbal medicine related hepatitis all over the world is shown in Table 1. We collected information of year happened, country, age (years old), gender, herbal substance, Glutamic oxaloacetic transaminase (GOT) (IU/L), total and direct bilirubin (mg/dl), days to recover (days), and mortality or not, and analyzed systemically.

2.1. Classification of herbal hepatotoxicity

Liver injury was defined by alanine aminotransferase (GPT), alkaline phosphatase (ALP) and R ratio equal to the ratio between GPT and ALP relative their respective upper limits of normal ranges (ULN), and classified as below

1. Hepatocellular type injury: if $R \geq 5$ and $GPT \geq 2 \times ULN_{GPT}$
2. Cholestatic type injury: if $R \geq 2$ and $ALP \geq 2 \times ULN_{ALP}$
3. Mixed type injury: if $2 < R < 5$ and both $GPT \geq 3ULN_{GPT}$ and $ALP \geq 2 \times ULN_{ALP}$.

These enrolled literature are from France (n=13), Germany (n=12), Switzerland (n=5) United States of America (n=4), Korea (n=4), Hong Kong (n=4), Greece (n=3), China (n=2), Canada (n=1), Italy (n=1), Thailand (n=1), Finland (n=1), Taiwan (n=1), and Japan(n=1).

![Figure 1. The process of enrollment 53 hepatitis after using herbal medicine (HILI). HILI=herb-induced liver injury.](image)

2.2. Statistical analysis

The data were analyzed with a commercial statistical software Stata/SE 12.0 program Stata Corporation, College Station, TX. Statistical $\chi^2$ tests were performed and the significance was set at a $P$ value of less than .05 (2-tailed).

3. Results

The 53 cases last from the year 1986 to 2016. The majority of cases are reported in France (24%) and Germany (23%), followed by Switzerland (9%), the United States of America (8%), Hong Kong (7%), Korea (7%), and Greece (6%). There are also cases report in China, Canada, Italy, Thailand, Finland, Taiwan, and Japan (Fig. 2).

The most commonly reported herbal medicine related hepatitis are Greater celandine reported in Germany (20.8%) and Germander reported in France (18.9%). The other contributing herbal medicine also include Seeds of Psoralea corylifolia (Boh-Gol-Zhee), Teucrium polium L., Chaparral leaf, Herbalife, Teucrium chamaedrys, Arrowroot juice, Bee pollen, Camellia sinensis, Carp juice, Ceramium kondoi, Chelidonium majus L., Cinnamon, Corydalis speciosa, Dai-saiko-to (Da-Chai-Hu-Tang
Table 1

| Herb                                      | Country          | n   | Percent |
|-------------------------------------------|------------------|-----|---------|
| Greater celandine                         | Germany          | 11  | 20.8    |
| Germander                                  | France           | 10  | 18.9    |
| Seeds of Psoralea corylifolia (Boh-Gol-Zhee) | Hong Kong       | 3   | 5.7     |
| Teucrium polium L.                         | Greece           | 3   | 5.7     |
| Chaparral leaf                             | Korea            | 1   | 1.9     |
| Herbalife                                  | Switzerland      | 2   | 3.8     |
| Teucrium chamaedrys                        | France           | 2   | 3.8     |
| Arrowroot juice                            | Korea            | 1   | 1.9     |
| Bee pollen                                 | United States of America | 1 | 1.9 |
| Camellia sinensis                          | Germany          | 1   | 1.9     |
| Carp juice                                 | Korea            | 1   | 1.9     |
| Ceramium kondoi                            | Korea            | 1   | 1.9     |
| Chaparral+bee pollen                       | United States of America | 1 | 1.9 |
| Chaparral                                  | Canada           | 1   | 1.9     |
| Chaparral                                  | Finland          | 1   | 1.9     |
| Chelidonium majus L.                       | Italy            | 1   | 1.9     |
| Cinnamon                                   | United States of America | 1 | 1.9 |
| Corydalis speciosa                         | Korea            | 1   | 1.9     |
| Dai-saiko-to (Da-Chai-Hu-Tang in Chinese)  | Japan            | 1   | 1.9     |
| Dandelion plantain, rocket and root vegetables, Ganoderma lucidum lingzhi, Glucosamine sulfate, chondroitin sulfate, Pax Ginseng, Shou Wu Pian, Teucrium viscidum, Tinospora crispa, and Xiao-chai-hu-tang (Table 1). The ages are ranged from 15 to 78 years with the mean ± SD (standard deviation) of 48.3 ± 16.2 years old. The majority of cases are female (n = 37). In elderly, male is more commonly seen than female in HILI (37.5% vs 10.5%, P = .02). Female is vulnerable to cholestatic type of HILI than male (21.1% vs 0.0%, P = .04). Of all the cases in HILI, using pure substance are more commonly seen than mixed substance (P = .02). In gender, male patients have higher alanine aminotransferase (GPT) (IU/L) level in HILI than female ones (1560 ± 819 vs 1047 ± 706, P = .03) (Table 2 and Fig. 3). There is no statistical significance in white blood cell count (micro-L), glutamic oxaloacetic transaminase (IU/L), total bilirubin (mg/dl), alkaline phosphatase (IU/L), days to recover, and mortality in gender comparisons in hepatitis after herbal medicine (Table 2).

4. Discussion

4.1. Age and gender

There are many theories about the pathogenesis of liver injury after using herbal medicine. Raschi et al have divided the suspicious pathogenesis into three main related factors: host, drug, and environments. A similar concept in DILI, Robert et al implicated the similar pathogenesis of idiosyncratic DILI, included age, gender, genetic, drug-drug interaction, drug dosage, and the environmental factors. In the host factors, we find in the elderly group, the male is more vulnerable to herbal toxicity than female. As in DILI, the male is tent to overreacted in specific drugs such as anti-viral drug and...
azathioprine than women.\textsuperscript{[8,10]} However, some reviews described the different opinions, the older female tend to get liver injury after using non-body-building HDS.\textsuperscript{[11,12]} Rolf Teschke et al also reported the female is the predominates gender in HILI and in a Korea study, all the cases above 50 years old identified with HILI were all females.\textsuperscript{[7,13]} Females are believed to sensitive to specific drugs as specific antibiotics and some antipsychotics agents.\textsuperscript{[14]} Shapiro et al also reported the elderly and the women are more commonly seen in liver injury caused by any medication.\textsuperscript{[15]} In our study, female accounted for 69.8% cases of HILI, but in the elderly, male is predominant in HILI. Considering in the old age, gender may have different susceptibility in HILI which need more studies in the aging population in the future.\textsuperscript{[9]}

### 4.2. Prevalence

TCM has many alternative names such as complementary and alternative medicines (CAMs), traditional Asian medicine (TAM) or traditional oriental medicine (TOM), and Kampo Medicine in Japan. CAMs, focusing on herbal usage, is a very popular traditional medicine in China for over thousands of years, though its treatment efficacy cannot be proven. TAM is still a very popular medication and becomes more and more popular in years worldwide. We surprisingly find there are only 2 cases reported in HILI of China were included in our study. Yuan Zhoua et al had announced a Chinese literature research for DILI and HILI, revealed the TCM related liver injury often classified into the “drug” induced liver injury, not HILI.\textsuperscript{[16]} Yuan Zhoua et al also considered the epidemiology of Chinese medicine

**Table 2**

|                      | Male (n = 16) | Female (n = 37) | Total (n = 53) | P value |
|----------------------|--------------|----------------|---------------|---------|
| Age (years old)      | 52.1 ± 19.4  | 46.7 ± 14.6    | 48.3 ± 16.2   | .27     |
| Elderly n (%)        | 6 (37.5)     | 4 (10.5)       | 10 (18.9)     | .02*    |
| Cholestasis n (%)    | 0            | 8 (21.1)       | 8 (15.1)      | .04*    |
| Substance,           |              |                |               |         |
| pure n (%)           | 10 (62.5)    | 33 (89.2)      | 43 (81.1)     | .02*    |
| mixture n (%)        | 6 (37.5)     | 4 (10.8)       | 10 (18.9)     |         |
| WBC (White blood cell count (micro-L)) | 7536 ± 2900  | 6790 ± 2502    | 7077 ± 2569   | .63     |
| Glutamic oxaloacetic transaminase (GOT) (IU/L) | 1194 ± 583   | 1009 ± 873     | 1054 ± 790   | .52     |
| Alanine aminotransferase (GPT) (IU/L) | 1560 ± 819   | 1047 ± 706     | 1205 ± 773   | .03*    |
| Total Bilirubin (mg/dl) | 9.5 ± 8.5    | 13.3 ± 16.7    | 12.0 ± 14.8   | .41     |
| Alkaline Phosphatase (ALP) (IU/L) | 220.0 ± 127.9 | 267.9 ± 186.0  | 253.2 ± 170.4 | .35     |
| Days to recover (days) | 56.6 ± 31.2  | 86.1 ± 65.6    | 78.0 ± 59.4   | .14     |
| Admission (n)        | 13           | 27             | 40            | .52     |
| Mortality (n)        | 0            | 1              | 1             | .51     |

\(^{*}\) indicates reaching statistical significance.
related liver injury in China, not being well recognized.[14] A
review article written by Melchert et al, among 1307 patients
who received TAM, only 2 patients were recognized symptom-
atic.[15] In Asian countries, such as China and Korea, the etiology
in HILI and DILI, may not be well described, resulting in
relatively lower frequency in China, and may not meet the global
classification of liver injury type as used in Europe or USA, where
showed progression in the usage of HDS over the last 10
years.[18–20] For the reason above, Gaby Danan et al strongly
recommend China to report HILI cases with precise assessment as
(Roussel Uclaf Causality Assessment Method) RUCAM and
should exclude all the possibility that might cause liver injury.[21]

Nowadays, there are many studies in genome-wide association
(GWA) approaching genetic pathogenesis in HILI and DILI.[7]
Daly AK et al discovered the human leukocyte antigen (HLA)
gene is strongly associated with DILI which caused by
flucloxacillin.[22] HLA-B*5701, an immune-related gene, consid-
er playing an important hypersensitivity-mediator in the
overreaction to abacavir, resulting in severe adverse drug
reactions as acute liver failure, which prevalence in Europe.[7,23]
This is compatible with our study discovered the major
prevalence of HILI in Europe rather than Asia. In our study,
HILI cases in Europe are 2.75-fold Asia (66% vs 24%).

4.3. Classification into hepatocellular, cholestatic injury,
and mixed type

Similar to DILI, Teschke R et al consider the mechanism of HILI
can be classified into idiosyncratic and intrinsic injury. Idiosyn-
cratic injury, which dosage independent, can further subclass into
metabolic type and immunologic type.[24] For example, the top 2
herbals account for almost 40% of HILI cases in our study are
Greater celandine (n = 11, 20.8%) and Germander (n = 10,
18.9%), both classified in the metabolic type of idiosyncratic
injury, due to their liver-toxicity metabolites. But Benninger et al
had done a case series for hepatitis after Greater celandine
ingested and consider the greater celandine may also have
immunologic toxicity due to the titer of antibodies.[25] It is very
cumbersome and complicated process of making herbal and
other supplements. And the possibility of toxicity in herbal
included mistaking the wrong herbs, not appropriate collections,
not suitable manipulation, poor preservation, inappropriate
extraction may associate with herbal toxicity.[26] Although most of
the herbs toxicity remains unclear, we can assess the herbal
toxicity through lab criteria which included alanine aminotrans-
ferase (GPT), alkaline phosphatase (ALP) and the ratio between
GPT to ALP relative their respective upper limits of normal
ranges (ULN).[12] Hepatocellular injury is the dominant liver
injury type in herbal toxicity which meets the below criteria as[11]
GPT 3 times above ULN of GPT[2] R ratio over or equal to 5. The
cholestatic injury is defined as[1] ALP 2 times ULN of ALP[2] R
ratio <2.[12,24,27] According to our research, we find the women
is the predominant gender in cholestatic injury after herbal usage
than men (P < .05). In Björnsson et al reported several drug-
induced liver diseases, the female is accounted for 59% of the
cholestatic types.[14] Russmann et al also found Flucloxacillin
associated cholestatic type DILI is most seen in women.[28] But
the study in the USA showed no significant gender difference in
cholestatic type of DILI.[29]

HILI has similar mechanisms and symptoms with DILI. They
share almost identical clinical, biochemical, and histological
features of hepatotoxicity.[30] Conventional synthetic drugs
usually have well-established liver injury mechanisms and
identified compounds that involved. Classification of herbal
hepatotoxicity is challenging to define because the herbal product
is often a combination of various constituents and involves
various confounding variables.[31]

HILI can be broadly categorized as intrinsic vs idiosyncratic,
and the latter further classified into allergic vs non-allergic.[32]
Intrinsic hepatotoxicity is dose-dependent and predictable above
specific thresholds. The intrinsic toxicity of the herbs is dosage
causing severity of liver injury. In contrast, idiosyncratic
hepatotoxicity is usually unpredictable happened without
dose-related respond. Allergic idiosyncratic hepatotoxicity
involves adaptive immune reactions with the presence of typical
symptoms such as fever, skin reactions, eosinophilia, and the
formation of autoantibodies, and a short latency period in
particular after re-challenge.[32] The risk of acute liver failure
associated with idiosyncratic hepatotoxicity is usually less than 1
per 10,000 patients.[32]

The pathophysiologic mechanism of drug-induced hepatotoxici-
ity can be divided into hepatocellular and extracellular
processes.[32–34] Hepatocellular process start from covalent
binding of a substance to intracellular proteins results in a
decrease in adenosine triphosphate (ATP) levels and actin
disruption, cause cell swollen and rupture. If substance covalent
to cytochrome P450 enzyme results in immunogens activating T-
cells and cytokines formation, and evoking consequence immune
response. Tumor necrosis factor (TNF) activation apoptotic
pathways to hepatocytes results in programmed cell death.
Extracellular processes include disruption of the transport proteins
cause interruption of transport systems, result in the impairment
of canalicular transport of bile salts and cholestasis. Besides, toxic
metabolites excreted in bile may further destruction bile duct
epithelium. Hepatic biochemistry pattern of HILI can be
categorized into three types: hepatocellular, cholestatic, or mixed
pattern.[34] Hepatocellular type represents hepatotoxicity are
mainly hepatocellular process, while cholestatic type are extracel-
larular process, and mixed type are the combination of 2 processes.

4.4. Significance of results

Our study collects 53 cases with pure or mixed substances herbal
product, the 3 most frequently reported hepatotoxic herbal
products are greater celandine (n = 12, 22.64%), germander
(n = 12, 22.64%), and chaparral (n = 5, 9.43%). We discuss them
as below.

4.4.1. Greater celandine. Greater celandine (Chelidonium
majus L.) is a plant of the poppy family that grows wildness
in Asia and Europe.[33] It has been used for centuries to treat
gastrointestinal complaints, dyspepsia, and gallbladder disease.
Several cases of liver injury associated with greater celandine have
been reported, mostly from Germany.[35–40] Lobular and portal
inflammation with bridging fibrosis and eosinophilic infiltrates
were observed in most of the liver histology.[25] More than 20
different kinds of alkaloids can be found in greater celandine,
including chelerythrine, sanguinarine, berberine, chelidonine,
and coptisine.[40] However, hepatotoxicity cannot be found by
each of them. Because there is no evidence of dose dependency,
and with long and variable latency as well as the presence of
eosinophilic infiltrate, hepatotoxicity related to patient’s idiosyn-
crasy also considered by investigators.[35,41]

4.4.2. Germanders. Germanders (Teucrium chamaedrys L.)
are found in Europe and the Middle East, and the aerial parts of
the plant are used.[42] Germander has been used for centuries as
traditional herbal remedies for their diuretic, diaphoretic, antipyretic, antispasmodic, anti-inflammatory, antihypertensive, anorexic, analgesic, hypoglycemic, and hypolipidemic properties. [43, 44] Germander has become popular as a remedy for weight loss in the past few decades. [45] In 1986, germander-containing capsules and tea preparation were approved in France as an adjuvant to weight control. But after several advert incident germander-associated acute, chronic, and even fulminant hepatitis, the remedy was withdrawn from the market and banning it in 1992. [46, 47] In general, germander-induced hepatotoxicity may occur after approximately 2 to 3 months of ingestion at the manufacturer’s recommended doses (600–1600 mg/day). Symptoms related to hepatotoxicity are non-specific and typically include fatigue, nausea, and the development of jaundice associated with marked elevation of serum aminotransferase levels. [48–49] the typical features of hepatocellular adverse reactions.

4.4.3. Chaparral. Chaparral (Larrea tridentata), commonly known as creosote bush or greasewood, is a botanical dietary and “energy” supplement. It is prepared from the leaves of the evergreen desert shrub that can be found in the southwestern U.S. and Mexico. [50] Native Americans have traditionally used it medicinally for the treatment of various ailments including respiratory tract infections, rheumatic pain, abdominal pain, chicken pox, and snakebite pain. [51] Currently, chaparral has been marketed in the form of tea, capsules, and salves (for burns), weight loss, liver tonic, blood purifier, and treatment of skin disorders. [51] In the 1990s, a series of incidents regarding chaparral-associated hepatotoxicity were reported to the FDA. [52] The hepatotoxicity of chaparral is generally attributed to nordihydroguaiaretic acid (NDGA). NDGA is an antioxidant and was once used as a preservative in foods for humans and for pharmaceuticals. NDGA can inhibit lipoxygenase and cyclooxygenase, [53, 54] and hence, it affects many intrahepatic pathways. The predominant pattern of liver damage was cholestatic hepatitis with high serum transaminases and the elevation of bilirubin and alkaline phosphatase. [54] Liver injuries ranging from mild hepatitis to cirrhosis and fulminant liver failure were reported. [51]

4.5. Laboratory tests
In total bilirubin value, there is no significant statistical difference between the 2 gender groups. Alanine aminotransferase (GPT) is a primary indicator for hepatocyte damage severity in biochemistry, and in our study, male victims have higher average GPT than female (1560 ± 819 vs 1047 ± 706, P = .03). Due to the male group has a higher portion of elderly (37.5% vs 10.5%, P = .02), we consider the result represent elderly people are generally at a higher risk for HILI or DILI. According to other authors’ hypothesis, older age patients have decreased hepatic and renal clearance, higher probability of drug-to-drug interactions, reduced hepatic blood flow, variation in serum drug binding, and lower hepatic volume. [55] Eight patients were classified as cholestatic and mixed type hepatotoxicity, and all of them are female. A report in 2009 from Spain described that older age is a determinant for cholestatic damage with a male predominance, and cytolitic damage is associated with younger female. [56]

4.6. Days to recover and outcome
Patients who recover from herbal-induced hepatotoxicity generally have a favorable prognosis. Average days to recover from HILI in our study is 78.0 ± 59.4 days, without reaching statistical difference between genders (56.6 ± 31.2 vs 86.1 ± 65.6, P = .14). Most of the patients (n = 40) need to admission for supportive care, with a similar proportion in two groups (13 vs 27, P = .52). Only one female case in our study suffered acute liver failure and mortality.

4.7. Prevention
Although the hepatotoxic potential of herbal products has been recognized for years, there is a definite lack of reliable population-based epidemiological studies specifically relating to the incidence of herbal hepatotoxicity. Herbs are considered by food and dietary supplement and had a lower threshold of required evidence for safety. [57] In the U.S., the Dietary Supplement Health and Education Act (DSHEA) of 1994 was an amendment to the US Federal Food, Drug, and Cosmetic Act (FD&C). [52] The DSHEA requires that manufacturers establish product safety before marketing. Manufacturers must ensure that the product label is truthful and not misleading. The label must contain a complete list of all ingredients contained in the product and the identity of the manufacturer. Herbal products that were already in distribution prior to 1994 are allowed on the market, the safety can only depend on user experience without scientific evidence. For these reasons, the National Library of Medicine and the DILI Network study group has established the LiverTox website. [58]

This online database contains more than 1000 products that have been implicated DILI with comprehensive clinical information for both the general physician and the specialist. However, we believe plenty amount of HILI incidents were never reported due to causality assessment is challenging. Clinicians should keep in mind to take a history of herbal products to use while evaluating a patient with abnormal liver function.

5. Conclusion
Herbal and dietary supplements are popular all over the world, and herbal medicine usages are not only Asian countries but also Europe and Americans. In hepatitis after using herbal medicine (HILI), the female is more commonly seen than male, but less than male in the elderly. Pure substance more often happens to HILI than mixture substance. Female is predominant in the cholestatic type of HILI. The major prevalence of HILI is in Europe rather than in Asia. HILI cases in Europe is 2.75-fold than in Asia. This could be due to fewer reports of the herb induced liver injury in Asia compared to Europe. Prevention of HILI is the best policy because it needs to take 78 ± 59 days to recover.

6. Limitation
There are some confounding factors in this study. Because it is based on the PubMed search, and possibly there are some HILI cases unreported all over the world. Thus, it could be underestimated in number of HILI cases. After all, it is a retrospective study; some data losses are inevitable to influence the statistical result.

Author contributions
Conceptualization: Yu-Jang Su
Data curation: Nai-Hui Lin, Hsiu-Wu Yang, Yu-Jang Su, and Chen-Wang Chang
Formal analysis: Yu-Jang Su and Chen-Wang Chang
Investigation: Nai-Hui Lin, Hsiu-Wu Yang, and Yu-Jang Su
Methodology: Nai-Hui Lin, Hsiu-Wu Yang and Yu-Jang Su, and Chen-Wang Chang.

Project administration: Yu-Jang Su

Resources: Nai-Hui Lin, Hsiu-Wu Yang

Supervision: Yu-Jang Su

Writing – original draft: Nai-Hui Lin, Hsiu-Wu Yang, and Yu-Jang Su

Writing – review & editing: Yu-Jang Su

Yu-Jang Su orcid: 0000-0003-0218-1944.

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[2] Department of Internal Medicine, College of Medicine, National Taiwan University Hospital, Taipei, Taiwan

[3] Corresponding author. E-mail address: <ghsuk@ntu.edu.tw> (G.-H. Su).

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