

Hepatotoxic Botanicals - An Evidence-based Systematic Review

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ABSTRACT – Purpose. Herbal medicines have been increasingly used worldwide. However, the potential harms of these herbs have been noticed most recently following hepatotoxicity with ingestion of herbal remedies. The aim of this review is to evaluate the evidence of hepatotoxic effects linked to use of herbal preparations. **Method.** Electronic search was performed by searching several databases: PubMed, HerbMed, Google Scholar, Scopus, Cochrane Database of Systematic Reviews and Cochrane Library using both Latin and common names of several herbs. Language was restricted to English and articles were selected for relevance reporting incidence of hepatotoxicity associated with use of herbal products in human. **Results.** From a total of 565 relevant reviews and articles, 254 met our inclusion criteria and were analyzed. Serious hepatotoxic events associated with various herbal products alone or in combination with other drugs have been reported. Linking to herbal constituents the spectrum of liver toxicity includes elevated liver enzymes, acute or chronic hepatitis, cholestasis, hepatic necrosis, fibrosis, and cirrhosis, as well as acute liver failure and hepatic veno-occlusive disease. **Conclusion.** The hepatotoxicity of herbs was extensively acknowledged. As the use of natural medicine increases, the risk of liver toxicity and drug interaction increase as well. Accordingly, herbal remedies have been known as hepatotoxins causing several liver damages. Further scientific studies with high and good quality are needed to identify toxic compounds and understand the exact mechanism of hepatotoxicity-induced by herbs. The adverse effects of herbal products must be fully reported as well as extensive education of healthcare providers must be provided in order to reduce danger of alternative medicines.

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INTRODUCTION

The use of alternative medicine or phytotherapy can be traced back in old manuscripts coming from ancient China, India, Iran, Korea and Egypt. During the past several decades, the use of herbal medicines has been expanded and gained more attention due to their therapeutic potentials (1,2). Certain factors contributed to the increasing use of herbal medicine including effectiveness, availability, affordability, and, apparently, safety (3). It has been estimated that over 500 herbal products are distributed as harmless healthy products worldwide (4). As compared to conventional therapy, natural therapy is believed to be free of side effects (5).

Liver is the largest and most vital organ in human body and able to detoxify several chemical compounds (6). The occurrence of liver toxicity cases linked to herbal medicine raises some concerns regarding herbal safety (7,8,9). According to two reviews, several case reports reported severe hepatic damage associated with botanicals alone or in combination with other medications (7,10). The toxicity of herbs is

probably due to several factors such as plant component that has been used, storage conditions of plant, mislabeling or misidentification of plant, and contaminations (11). Recently, different hepatic reactions involving botanicals have been documented (12). The spectrum of liver toxicity includes elevated liver enzymes, acute or chronic hepatitis, cholestasis, hepatic necrosis or fibrosis, cirrhosis, liver failure, and hepatic veno-occlusive disease (12,13). Some of botanicals that raised severe health concerns are Black cohosh (14), Chaparral (15), Saw palmetto (16), Comfrey (8), Germander (17) Kava (18) and many others as described in this review.

The purpose of this paper is to review already published cases and spontaneous reports of the hepatotoxicity of each botanical and systemically assess the evidence of hepatotoxic events associated with these herbs as well as providing botanical names, synonyms, active constituents,

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potential herb-herb interaction or herb-drug interaction and possible mechanisms of toxicity.

METHODS

We reviewed scientific articles that were obtained from PubMed, HerbMed, Scopus, Google Scholar, the Cochrane Database of Systematic Reviews and Cochrane Library databases between 1900 and 2013. We used the following search terms: herbal hepatotoxicity, hepatotoxic plants, liver toxicity, botanicals hepatotoxicity, toxic hepatitis, herbal remedies, alternative medicine, complementary therapy as well as the common and Latin name of botanicals. The search was restricted to English language articles and Human studies only.

RESULTS

The search generated 565 relevant papers, of which 310 were excluded as shown in **Figure 1**. A list of herbs with hepatotoxic effects is shown in **Table 1**. Our search identified cases that provided evidence of hepatotoxicity of certain herbs. In addition, we indicated whether medicinal botanicals were alone or combined with other

drugs implicated in several hepatotoxic incidents. Moreover, several possible mechanisms of herbs causing hepatotoxicity appear to be involved and are summarized in **Table 1**. In some case reports we did not find enough scientific documentation and limited information of several herbs was provided. However, we combined the knowledge derived from phytotherapy and liver metabolism to provide a unique comprehensive guide for pharmacologists and pharmaceutical scientists.

Black cohosh (*Actea racemosa*):

Actea racemosa is a perennial, woodland herb with a thick root system (rhizome) that belongs to Ranunculaceae family and is native to North America (Figure 2A) (19). *Cimicifuga racemosa* is one synonym of this plant and other names include black coach, black snakeroot, rattleroot, bugwort, macrotys and bugbane (20). The root of black cohosh has been used by Native American Indians for treating several conditions like colds, coughs, fatigue, and constipation (21). In particular, cimicifuga rhizomes have been used as treatment for menopause-related symptoms, rheumatism, dysmenorrhea, and premenstrual discomfort (21,22).

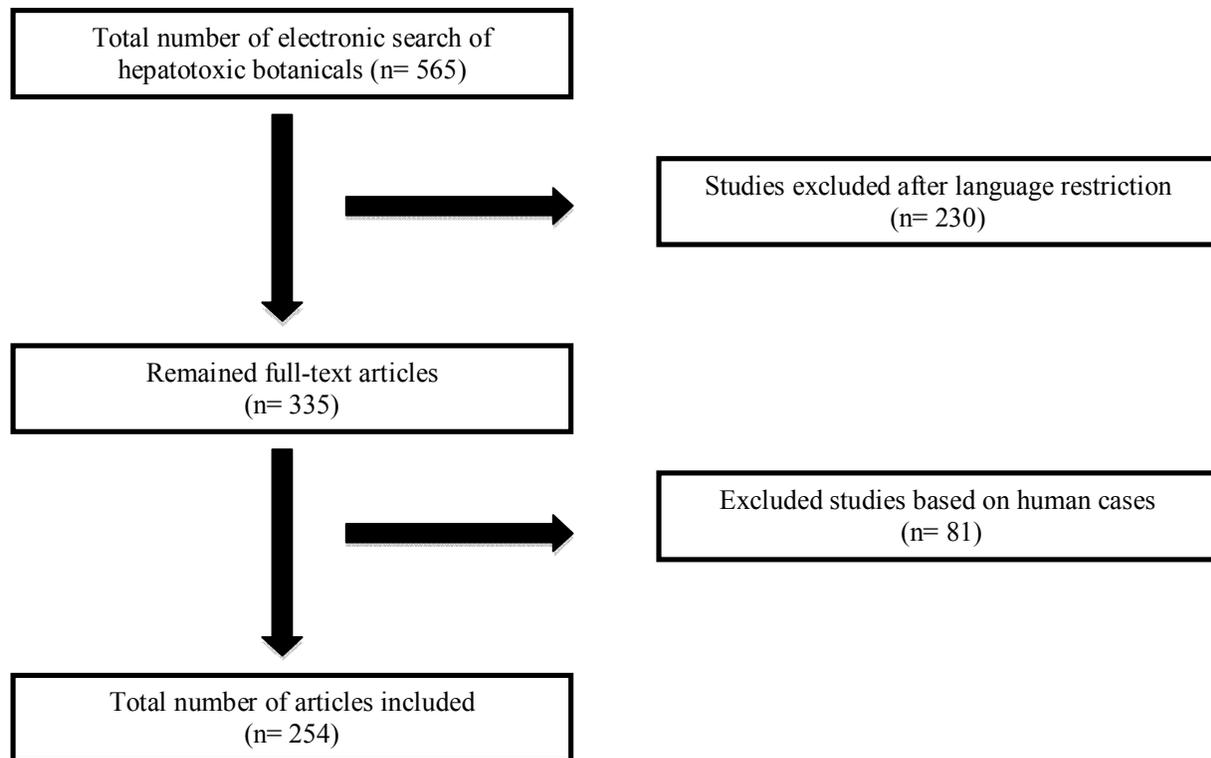


Figure 1. Flow chart.

The main active constituent of black cohosh rhizome is terpene glycosides like actein, cimicifugoside and 27-deoxyactein as well as some other active constituents like alkaloids, flavonoids and tannins (23). Several studies have been conducted to determine the safety of black cohosh. Some of these studies suggested that Cimicifuga extract causes severe acute hepatitis and liver failure and autoimmune mechanism has been proposed (14,24,25). In fact, Cohen et al. (25) reported the first case of autoimmune hepatitis associated with the use of black cohosh in a 57-year-old woman without history of liver disease. She started to use black cohosh to treat "hot flashes", but she developed autoimmune hepatitis. Another case report mentions a relationship between the use of cimicifuga and acute hepatitis (14). A 47-year-old woman with no history of liver disease took black cohosh for one week with no other medication to treat menopause symptoms. Severe hepatitis and jaundice developed following ingestion leading to liver transplant. In the report by Levitsky et al. (24), a 50-year-old woman had black cohosh root daily as a medication for menopause symptoms. The patient was admitted to the hospital for liver transplantation due to development of acute fulminant hepatitis with diffuse cell necrosis and cholestasis.



Figure 2: Hepatotoxic Plant (A) Black Cohosh (*Actaea Racemosa*) (26)

Chaparral (*Larrea tridentata*):

Chaparral is an evergreen desert shrub, which is made of leaves of greasewood or creosote bush (Figure 2B). It is native to the southwestern United States and Mexico (15,27). *Larrea tridentata* is the botanical name of chaparral and other synonyms include *L. glutinosa Engelm* and *L. divaricata Cav.* (28). Ancient Native Americans have used chaparral as tea to treat rheumatic pain and bronchitis. It also has been used in different forms like capsules and tablets for the treatment of other conditions such as diarrhea, cold, rheumatism, urinary tract infection, and chronic

skin diseases (29,30). Among herbs, chaparral is probably the best known antibiotic treatment derived from plants (31). Nordihydroguaiaretic acid (NDGA) has been proposed as the active constituent of chaparral. NDGA is an antioxidant and an inhibitor of two biochemical pathways involving cyclo-oxygenase and lipoxygenase (28,31). Some of reported side effects of chaparral include: vomiting, diarrhea, rash, fever, and abdominal cramp (28). Hepatotoxicity is the major problem linked to chaparral ingestion (32). A review done by Sheikh et al. (15) reviewed 18 cases of illnesses following chaparral ingestion. The age range of 13 patients was 25-60 and jaundice was the main sign of liver disease. Liver injury also included cholestatic hepatitis, fulminant liver failure, and rash progression to cirrhosis. In a 22 years old woman, the hepatotoxicity developed during the breast-feeding period following delivery of a healthy newborn and ingestion of chaparral to increase milk secretion (31). Her liver biopsy and lab findings confirmed the diagnosis of acute drug-induced hepatitis as well as hepatic fibrosis. Another report of a male individual of 27 years of age developed hepatitis after 12 month of taking chaparral to prevent illness (28).



Figure 2: Hepatotoxic Plant (B) Chaparral (*Larrea tridentata*) (33)

Saw palmetto (*Serenoa repens*):

Serenoa repens (*S. repens*), commonly known as saw palmetto or scrub palmetto, is the most common herb used for treatment of symptoms of benign prostatic hyperplasia (BPH) and urinary tract infection (UTI) (34). It is a dried ripe fruit of American dwarf palm tree that is native to West Indies and South-eastern America. It is also known as *Sabal serrulata* and *Serenoa serrulata* (botanical names) (Figure 2C) (35,36). The preparation of saw palmetto is called prostata and it is composed of fatty acids and phytosterols (37). The most active ingredients of saw palmetto

are steroidal and sitosterol compounds (35). Furthermore, saw palmetto has estrogenic and antiandrogenic properties (38). Obviously, both estrogen and antiandrogen can be hepatotoxic. In fact, high levels of estrogen are associated with cholestatic effects and antiandrogen effects include fulminant hepatitis (39,40). Few studies and case reports have reported some toxicity of *S. repens*. A case report reported the association between prostate and protracted cholestatic hepatitis in 65-year-old man taking this herbal preparation to treat nocturia and hesitancy (39). Additionally, Lapi et al. (41) reported a case of acute liver damage associated with saw palmetto. A 58-year-old man consumed a commercially available *S. repens* (2 capsules/day) as a treatment of BPH. He was previously diagnosed with Gilbert's syndrome, the most common hereditary cause of increased bilirubin present in 5-10% of the population due to reduced activity of the enzyme glucuronyltransferase, which conjugates bilirubin and some other lipophilic molecules. Gilbert's syndrome produces an elevated hematologic level of unconjugated bilirubin but normally has no serious consequences. After taking *S. repens*, the patient was diagnosed acute liver injury. According to other case reports, saw palmetto was linked to pancreatitis as well. In 2006, Jibrin et al. (16) reported a case of 55-year-old man who had saw palmetto for four years for BPH. He presented with severe epigastric pain, vomiting, and nausea. The patient was diagnosed with both acute hepatitis and pancreatitis due to saw palmetto. Bruminhent et al. (36), reported another case of acute pancreatitis following exposure to *S. repens*. A 61-year-old man with previous history of BPH and gastro-esophageal reflux disease developed acute pancreatitis resulting from saw palmetto ingestion with other drugs.



Figure 2: Hepatotoxic Plant (C) Saw palmetto (*Serenoa repens*) (42)

Comfrey (*Symphytum officinale* L.):

Comfrey is a common garden plant that belongs to Boraginaceae family (43). There are several species that belong to *Symphytum* genus, which includes *S. officinale* L. (comfrey), *S. asperum* Lepech, *S. caucasicum* Bieb, *S. tuberosum* L. and *S. x uplandicum* Nyman (43,8). The most commonly used species is *S. officinale* L. or comfrey, which is a long perennial plant that is made of small flowers that are purple in color and large hairy leaves (44,45) (Figure 2D). For more than 2000 years, comfrey leaves and roots have been used as medicinal herb (46). Additionally, comfrey has been consumed as tea and vegetable for the treatment of various diseases including bone fractures, wound healing, inflammation of joints, and thrombophlebitis (47,48). The major content of comfrey is pyrrolizidine alkaloids (PA), which is presented in higher concentration in roots than in leaves (49). Several studies reported health risk associated with PA. The major hepatotoxic effect of PA is the hepatic veno-occlusive disease (VOD) (50,51) that is also known as Sinusoidal obstruction syndrome (52). Portal hypertension with severe ascites is one of major characteristics of VOD disease (53). Epidemics of VOD were reported several decades ago in South Africa, Jamaica and India and Afghanistan (8). In a case report previously published by one of the authors (CS), bush tea containing pyrrolizidin alkaloids was consumed by the mother of a baby who presented at neonatal age with VOD and liver failure (54). This was the youngest patient with VOD ever described in the literature. Many case reports confirm indeed the toxicity associated with comfrey consumption. The first report of PA intoxication was in 1985 (50). A 49-year-old woman was diagnosed with portal hypertension with obliteration of small hepatic venules after taking 85 mg of PA for six months. Another recent case involved a 66-year-old woman that was previously diagnosed with chronic disease. She consumed around 1.5 L of comfrey tea, which caused progressive dyspnea. Subsequently, she developed severe pulmonary hypertension (55). Using comfrey leaves as vegetarian diet, a 23-year-old man reported to have VOD with severe portal hypertension and lastly died due to liver failure (56). Another case was a 47-year-old woman, who consumed ten cups of comfrey tea (10 cups daily) as well as comfrey pills for more than one year. After four years, she was diagnosed with ascites and her liver biopsy showed dense fibrosis of portal tracts as well as bile duct proliferation around the portal tracts of the liver

(57). Cases of comfrey-induced hepatic VOD were reported in young ages and infants beside older age patients. One case report of 13-year-old boy drank comfrey tea (unknown quantity) for his Crohn disease. Liver biopsy was done because of hepatomegaly and ascites resulted in hepatic VOD (58). Another case report of 18-month-old boy showed the evidence of comfrey-induced VOD in infants drinking comfrey herbal tea (53).



Figure 2: Hepatotoxic Plant (D) Comfrey (*Symphytum officinale* L.) (59)

Germander (*Teucrium chamaedrys* L.):

Teucrium chamaedrys L., also known as wall germander, is a small herbaceous, perennial and aromatic plant that belongs to the *Lamiaceae* family (Figure 2E) (5, 60). Germander belongs to the East Mediterranean basin and found in all European woods (60,61). Since ancient times, germander has been used as herbal remedy for several properties including antiseptic, antidepressant, diuretic, choleric, and tonic (5, 17, 60). Globally, wall germander has been used as capsules or teas for the treatment of obesity and as a weight-loss agent (13,17,60). Moreover, germander was considered safe until many cases of hepatotoxicity associated with germander ingestion were reported in France (62,63). Other side effects of germander include nausea, vomiting, anorexia, and jaundice (63,64). *Teucrium chamaedrys* L. contains many chemical substances including glycosides, saponins, neoclerodane diterpenoids, and flavonoids (5,13,60). Neoclerodane diterpenoids are the major chemical compound that may cause liver injury. Additionally, the hepatotoxicity may also be attributed to Teucrin A and teuchamaedryn A, which are components of the diterpenoids fraction (13,63,65). In 1992, the germander powder-containing capsules were prohibited and banned from the French market after an epidemic of 30 cases of hepatitis (13). Several case reports have reported the hepatotoxic effect associated with

germander ingestion (5,13,17,60). Larrey et al reported seven cases of acute hepatitis after germander ingestion (17). One of the cases involves a 54-year-old woman, who was taking germander capsules for weight loss and developed hepatitis. However, after six months of germander discontinuation, the women showed a complete recovery of the liver function. Larrey et al. also reported another case with hepatitis. A 15-year-old female adolescent, who had abdominal pain and developed hepatitis with jaundice after taking germander capsules (600 mg/day) for few months in combination with other drugs. She recovered after one month of germander discontinuation (17). Laliberte et al. (5) reported two cases of germander-induced hepatitis. The first case is a 55-year-old woman with no history of liver disease who took germander capsules (1600 mg/day) as a medication for hypercholesterolemia with some other drugs. She developed jaundices after six months of germander intake and diagnosed with hepatitis. However, the liver function tests of the patient improved after two months germander was discontinued. The second case involved a middle-aged woman used germander (260 mg/day) for 6 month to reduce her weight and was diagnosed with jaundice, asthenia, and hepatitis. Additionally, there is a case of 68-year-old woman who developed massive hepatic necrosis following ingestion of 450 mg daily of wild germander for two weeks (66).

Kava (*Piper methysticum*):

Kava, which is also known as ava, intoxicating pepper, awa, kava pepper, kawa, kava root, kawa, and kew, is a tropical shrub plant that belongs to the Piperaceae family (Figure 2F) (18,68,69). It has been traditionally used for centuries in South Pacific Islands (Hawaii, Polynesia and Fiji) for ceremonial purposes and as a remedy for psychotropic conditions (70,71).



Figure 2: Hepatotoxic Plant (E) Germander (*Teucrium chamaedrys* L.) (67)

For more than 2000 years, south pacific Islanders used kava-kava drink from kava plant without known side effect (72). Moreover, kava has been used by Western as an alcohol replacement to reduce anxiety and give relaxation feeling and as a treatment for sleeplessness, menopausal symptoms and depression (70,73). Rhizomes and roots of kava plant were the most used parts for their psychoactive properties that include sedation, anxiolysis and relaxation (74). Accordingly, the most active constituent of kava is kavalactones or kavapyrones, which is present in high concentration in roots. Kava lactones involve six major lactones (*kavain*, *dihydrokavain*, *methysticin*, *dihydromethysticin*, *yangonin*, and *desmethoxyyangonin*), which are responsible for pharmacological activity in humans (75). Even though kava known to have no side effects in the past, the first report of its side effects were reported in Europe (76). Moreover, hepatotoxicity associated with kava ingestion was also reported in Germany when 24 cases were diagnosed with severe liver injury (73). Whitton et al (73) indicated that the toxicity of kava was due to the extraction methods of lactones and posology of this natural product. Several cases reported the severe hepatotoxicity of kava leading to hepatitis, hepatic necrosis, and cholestatic hepatitis (70). Humberston et al (68) reported a case of acute hepatitis associated with kava-kava ingestion in a 14-year-old girl. A liver transplantation was performed and she recovered. Fu et al. (18) reported another case of kava hepatotoxicity. A 45-year-old woman took kava as one tablet twice a day for 8 month and she was diagnosed with jaundice and hepatitis. The patient required liver transplantation and she recovered later. More reported cases of kava-associated hepatotoxicity came from Europe. Six patients were women aged between 22 and 61 years and two patients were men with age between 32 and 50 years took kava (60 mg- 240 mg/daily). They all required liver transplantation after they were diagnosed with fulminant hepatic failure (76-78). Another case of kava-associated hepatotoxicity involved a 50-year-old female, who had hepatic necrosis when she had 210 mg/day of kava for four months. The woman had a liver failure however, she lived after liver transplant once performed (79). There are some other cases with patients, who unfortunately did not survive (77).

Greater celandine (*Chelidonium majus* L.):

Greater celandine is a plant that belongs to

Papaveraceae family. It is an important herb for its therapeutic potential and it grows widely in



Figure 2: Hepatotoxic Plant (F) Kava (*Piper methysticum*) (80)

Europe and Asia (81). Some common synonyms are swallow-wort and bai-qu-cai (82). The dried aerial parts of greater celandine are used as a treatment for gastrointestinal tract disorders (81). Greater celandine extract has been used as a therapy for jaundice, cholelithiasis and biliary colic (83). Additionally, it is known to have spasmolytic and alleged choleric properties (84). The whole plant found to have several different alkaloids; however, the main alkaloids are benzophenan thridines and protoberberines. Other common alkaloids are hydroxycinnamic acid derivatives (81). The potential hepatotoxicity of greater celandine has been reported in several case reports. Accordingly, analysis of case reports of 21 patients (18 females aged between 22-67 year-old and 3 males aged between 58-69 year-old) showed the causality of hepatotoxicity induced by greater celandine (85). There were high causality levels for greater celandine in two patients and low levels in 13 patients, where in the other 6 patients the causality was probable. Furthermore, this assessment of case reports associates the use of greater celandine preparation with liver injury. Stickel et al. (84), provided two cases of hepatotoxicity linked with *C. majus*. The first case involved a 39-year-old female who diagnosed with impaired hepatic synthetic function after ingestion of greater celandine-containing product as well as sulfamethoxazole antibiotic and penicillin.

However, the patient fully recovered after discontinuation of the herbal preparation. The second case involved a 69-year-old man developed cholestatic hepatitis after intake of greater celandine-containing drug for 6 weeks for his abdominal discomfort. The patient completely recovered. Moro et al. (81), reported another case of *C. majus* inducing hepatotoxicity. A 65-year-old man drank a cup per day of greater celandine

for a month with lansoprazole medication for his bacterial infection. He developed acute cholestatic hepatitis with high levels of transaminase and bilirubin, but he recovered completely after withdrawal of both drugs. Additionally, a 37-year-old woman diagnosed with cholestatic hepatitis after ingestion of several herbal preparations including greater celandine for 3 months for her atopic eczema. The woman stopped taking greater celandine but continued with other medications and she recovered (86). Moreover, greater celandine showed to cause phototoxicity and cytotoxicity on cancer cells (87, 88).

***Atractylis gummifera*:**

A. gummifera is an herbaceous and thorny plant (Asteraceae family) that belongs to Mediterranean countries (30,89). It is also known as blue thistle, bird-lime, chamaelon, acarna gummifera and carlina gummifera L. (89,90,91). A glue-like substance with whitish-yellowish color is secreted from this plant. *A. gummifera* root extract is commonly used as antipyretic, diuretic, emetic and purgative as well as chewing gum (92,93). However, it is a well known life-threatening poisoning (89). The intoxication with *A. gummifera* was first described by Lefrane since 1866 (90). The major toxic constituents are two diterpenoid glycosides: atractyloside (ATR) and carboxy-atractyloside (CATR) (90,91). Several case reports of *A. gummifera* inducing toxicity were reported and most victims were children because of sweet taste of the juice of this herb (94). One case report reported intoxication associated with consumption of *A. gummifera* rhizome in two children aged 4 and 6. They both presented with vomiting, abdominal colic, cyanosis as well as coma. They were diagnosed with congested intestine and had haemorrhages in stomach and kidney. The following morning, both children died (91). Another case of 7-year-old boy presented with vomiting and epigastric pain after drinking *A. gummifera* extract for treating oxyuriasis. The boy's condition worsened and died (95).

***Impila (Callilepis laureola)*:**

C. laureola is an herbaceous perennial plant that belongs to Compositae family (96). It is native to KwaZulu-Natal region of northeast of South Africa (97). *C. laureola* is commonly known as Impila that means "health" in Zulu (97). Impila has been traditionally used as a remedy for stomach problems, infertility, cough and worm infection (96). Additionally, *C. laureola* was used to ward off the evil spirits (98). It is known to be

highly toxic and very poisonous plant that is responsible for several deaths (99). Similar to *A. gummifera*, *C. laureola* contains toxic atractyloside (100). In South Africa, *C. laureola* has been linked with some cases of hepatitis and renal tubular necrosis (101). Moreover, an analysis of 50 children with Impila intoxication was done (102). The age of children ranged from 0 to 12 years and they were diagnosed with hypoglycaemia, hepatic dysfunction, renal dysfunction and alteration in consciousness level. Another case involved a mother (21-year-old) and her daughter (1-year-10-month-old) who consumed Impila and developed a toxic reaction. The mother died due to hepatocellular necrosis whereas the child recovered (98).

Chinese Herbal Remedies:

Chinese Herbal Medicine (CHM) has been known for more than 4000 years and was first found by Dhen Nung (103). CHM has been extensively used for centuries as a treatment for different diseases and conditions (104). However, the use of Chinese medicine raised serious concerns regarding safety due to unknown composition and amount of plants used (94). There are several hepatotoxicity effects have been associated with different Chinese herbal remedies. Moreover, the toxicity of CHM can be attributed to either one or several components (94). One of the commonly used herb in China is Jin Bu Huan (*Lycopodium serratum*), which has been used for centuries as analgesic, sedative and sleeping aid (30). Accordingly, Jin Bu Huan (JBH) reported to cause various hepatotoxic events (94,105). It contains a single active constituent that is the extract of *Lycopodium serratum* (94,106). Additionally, three females were diagnosed with acute hepatitis after consumption of JBH that was purchased from the same store (105). The first case involved a 66-year-old female who consumed 2 tablets (three times per week) as a treatment for her back pain and insomnia. The second patient (24-year-old) used JBH as a treatment for her insomnia (four times per week). She presented with jaundice, excoriations of her limbs and tender hepatomegaly. The last case involved a 45-year-old female presented with tender hepatomegaly and used JBH from three to four times per week for her insomnia along with another herb called "Ma Huang". Moreover, all the patients recovered after discontinuation of herbal preparations. Another hepatotoxic effect of JBH involved a 49-year-old male diagnosed with chronic hepatitis as well as moderate fibrosis after ingestion of three tablets of JBH per day (107).

His liver function tests returned to normal after discontinuation of JBH. Additionally, a case of 7 patients aged between 24-66 years old who used JBH and presented with fatigue, vomiting, nausea, fever and jaundice. They took from 2 to 6 tablets of JBH weekly (2-7 times) for treating insomnia, back pain and arthralgia. The all developed acute hepatitis due to JBH intake (108). Another common Chinese herbal remedy is Ma Huang, which is a product that derived from the aerial parts of *Ephedra sinica* plant that found in Mongolia and China (109,110,111). Ma Huang is known in English as “Yellow astringent” and has been traditionally used in China for the treatment of bronchitis and cough and as a slimming aid (109,112,113). Additionally, this medicinal herb has been used to enhance energy levels (110). Despite the prolong use of *Ephedra* in Chinese traditional medicine; it has been linked to many serious hepatotoxic effects (110,111,114,115). The major constituent in Ma Huang that is responsible for toxic effects is Ephedrine (110). Accordingly, Ephedrine showed to cause severe acute hepatitis in 33-year-old woman who used Chinese herbal medicine containing Ma Huang (110). Another hepatotoxic case associated with Ma Huang consumption involved a 28-year-old man who had Ma Huang for 2 month for bodybuilding. He developed hepatitis and recovered after discontinuation of herbal product (114). Ma Huang hepatotoxicity was seen in 44-year-old man who had over the counter drug called “Hydroxycut” for weight loss (3 capsule for 4 months). The man developed toxic hepatitis due to Hydroxycut, which found to contain Ma Huang extract. However, the patient recovered after cessation of the drug (115). Moreover, a 61-year-old man drank Ma Huang infusions and presented with hepatorenal syndrome as well as several thromboembolic conditions (116). Another case of Ma Huang related hepatotoxicity involved a 57-year-old woman who took two Chinese herbal products (one contains Ma Huang) for the treatment of sinusitis. The woman developed jaundice and acute liver failure and recovered after liver transplantation was done (109). Additionally, Ma Huang has been associated with high blood pressure and high heart rate in 42-year-old male who took *E. sinica* along with *Saw palmetto* and multivitamins for bodybuilding (117). The patient was diagnosed with hypertension and tachycardia due to ingestion of this herbal product. Lastly, a 23-year-old male student found dead in his apartment after consumption of Ma Huang-containing drink once or twice per day for more

than 6 month (118). Moreover, Shou-Wu-Pian is another common Chinese herbal mixture. Shou-Wu-Pian preparation is formulated from the root of *Polygonum multiflorum* plant (fleece flower root), which is a common Chinese herb that belongs to Polygonaceae family (113,119). Shou-Wu-Pian is alternatively known as He-Shou-Wu and Mr. Black Hair (119,120). The roots and vines of *P. multiflorum* have been used as a tonic for treating several conditions including backache, constipation, dizziness, greying of hair, spermatorrhea, lumbago and treating symptoms of chronic prostatitis (120,121,122). Shou-Wu-Pian has been well known for its association with longevity and youthfulness (120). Furthermore, several cases of hepatotoxicity associated with Shou-Wu-Pian consumption have been reported (112,121,123,124). The Shou-Wu-Pian hepatotoxicity has been attributed to its toxic constituent, anthraquinone (120). One of the reported hepatotoxic cases involved a 46-year-old woman who had an acute hepatitis after ingestion of Shou-Wu-Pian for greying of hair. She recovered after discontinuation of the herbal medicine (120). Another 53-year-old woman had toxic reaction due to Shou-Wu-Pian consumption and developed acute hepatitis. She also recovered after cessation of the herbal product (125). Additionally, Panis et al (119) reported the first case of Shou-Wu-Pian inducing hepatotoxicity in pediatric. A 5-year-old girl presented with acute liver injury twice related to Shou-Wu-Pian product. Another reported case of hepatotoxicity involved a 17-week pregnant woman who consumed Shou-Wu-Pian for treating hair loss. She presented with jaundice and diagnosed with acute toxic hepatitis (119). Moreover, a 78-year-old male used Shou-Wu-Pian for the treatment of chronic prostatitis and developed acute hepatitis. The patient recovered after discontinuation of the herbal medicine (121). Additionally, *Dictamnus dasycarpus* is another botanical that presents in Chinese herbal mixture (126). It belongs to Rutaceae family and has been used as a remedy for skin diseases, cough, jaundice and rheumatism (127). *D. dasycarpus* has been linked with some hepatotoxic events as well as death (10,128,129,130,131). One case of hepatic injury involved a 49-year-old female presented with itching and jaundice after drinking a mixture of Chinese herbal tea for her eczematous skin disease. Hepatomegaly and elevated liver enzymes were presented and the patient was diagnosed with reversible acute hepatitis due to intake of Chinese herbs. The analysis of Chinese mixture showed the presence of couple of

botanicals including *D. dasycarpus* (128). Another case of Chinese mixture toxicity involved 51-year-old male who previously had psoriasis and took a mixture of Chinese herbs daily for 8 weeks. His liver function tests were substantially elevated and he died (129). Moreover, a 61-year-old female took Chinese herbal preparations for 11 months as a remedy for eczema. The patient presented with jaundice, malaise, nausea, and weight loss. Her Chinese mixture found to contain a constituent of *D. dasycarpus* (130). Another case of a 39-year old female presented with anorexia, fatigue and nausea after ingestion of mixture of Chinese plants daily for 2 months to treat her psoriasis. The Chinese mixture found to contain *D. dasycarpus* as one of herbs (130).

Kampo Medicine:

Kampo medicine is a Chinese medicine that has been produced in Japan and it is a mixture of several herbs (111). Dai-Saiko-to or TJ-8 is a kampo formula that consists of seven herbs and used for the treatment of dyspepsia, fever, gallstones, fatigue, and chronic hepatitis (10,132). However, some reports reported cases of hepatotoxicity associated with consumption of Dai-Saiko-to. One case of hepatotoxicity included a 55-year-old female who took Dai-Saiko-to for 3 weeks and presented with fatigue, fever and increased liver enzymes. She was diagnosed with autoimmune hepatitis (132). Another case involved a 65-year-old man who ingested a 7.5 g of Dai-Saiko-to with other herbs included Shohusan and Hange-shashin-to for 7 weeks for treating his dermatitis. The patient presented with dyspnea and diagnosed with hepatic injury due to herbal preparation (10). Accordingly, the toxic agents presented in Dai-Saiko-to could be attributed to glycyrrhiza and scutellaria constituents (132). Another kampo herb is Syo-saiko-to, which has been used as a therapy for pyretic diseases and liver diseases in Japan, Taiwan, and China. It is also known as Xiao-chai-hu-tang or da-chai-hu-tang in China and TJ-9 in Japan (10,111,113,133). Syo-saiko-to consists of seven different botanicals including *Scutellaria* and *Glycyrrhiza* (111). Accordingly, some cases of hepatotoxicity have been reported due to intake of Syo-saiko-to. Four cases of four females aged between 42 and 58 had 7.5 g of Syo-saiko-to for up to 7 weeks as a therapy for acute hepatitis (134). They all presented with jaundice and diagnosed with inflammation of portal tract, fibrosis, microvesicular fatty change, acidophilic degeneration and two of them developed

cholestasis. The toxic compound in Syo-saiko-to for these cases found to be bicalin in *Scutellaria* and glycyrrhizin in *Glycyrrhiza* (133). Moreover, Syo-saiko-to showed to contain glycyrrhizin-a triterpenic saponoside- that causes liver diseases including fatal hepatic necrosis, hepatic granulomas and microvesicular steatosis (113).

Kombucha “mushroom” Tea:

Kombucha tea is a health drink that made by the fermentation of sweetened black tea with kombucha fungus, which is a symbiotic yeast-bacteria aggregate that surrounded by a permeable membrane (135,136); which is not a real mushroom (136). Kombucha has other synonyms such as Manchurian mushroom tea, Manchurian fungus tea or Kargasok tea (113,135). This healthy beverage has been used as therapy for several conditions like treating cancer, increasing T cell count, lowering blood pressure, curing arthritis, treating gastrointestinal disorders and alleviating constipation (135,136). Kombucha tea is also known as “fountain of youth” tonic as it restores the gray hair, reduces wrinkles and treats acne (136,137). However, kombucha beverage has been associated with several cases of hepatotoxicity and other side effects (135,138,139). A case of hepatitis due to intake of Kombucha drink was reported in a 53-year old professor (137). He drank the preparation as a half cup twice a day for two weeks that advised by his friend for treating his hypothyroidism and fibromyalgia conditions. However, he recovered after discontinuation of the Kombucha drink. Moreover, two females (59 and 48-years-old) reported drinking Kombucha beverage. The first patient had 4 oz daily for 2 months and developed severe metabolic acidosis and died. The second patient increased amount of tea from 4 to 12 oz daily for 14 days and developed acute pulmonary edema and severe metabolic acidosis. Additionally, the patient had cardiac arrest but her health improved (138). Another case of Kombucha toxicity involved a 22-year-old male who diagnosed with HIV and decided to use Kombucha tea as it known to increase the T cell count (139). The patient developed acute renal failure as well as hyperthermia and lactic acidosis after 12 hours of Kombucha intake. Furthermore, two females aged 55 and 51 drank Kombucha tea to improve their health; the first patient developed jaundice and second patient had breathing shortness, akathisia and shaking (135). Additionally, two men aged 53 and 83 drank Kombucha tea as one-half cup daily for 3 weeks and developed transaminitis (139). However, both

patients recovered after cessation of the beverage. The exact toxic agent of Kombusha mushroom is unknown but it showed to have usnic acid that is derived from lichen (106,113). However, its toxic reaction could be due to contamination of the tea. Moreover, preparation and storage of Kombusha tea must be made in glass containers as lead and ceramic can leach toxic components into preparation (140). Two cases of symptomatic lead poisoning due to Kombusha tea have been reported in one couple. They both drank Kombusha tea in ceramic container, which was covered by glaze made of lead (139).

Senna (*Cassia angustifolia*):

C. angustifolia, commonly known as Senna or Tinnevely, is a plant that is native to Arabia and belongs to Fabaceae family (141,142). The leaves (pods) and fruits of senna have been used as laxative in form of herbal tea (141,142). However, excessive abuse of *C. angustifolia* has been implicated in few cases of hepatotoxicity. Accordingly, a 26-year-old female was diagnosed with toxic hepatitis after intake of herbal tea containing 10 g of senna leaves and 100 mg of sennoside B (extract of senna fruit) twice a week (143). Another case of senna hepatotoxicity involved a 52-year-old woman who drank 1L of herbal tea containing 70 g of Senna dried fruit for more than 3 years. The patient developed acute liver failure with renal impairment due to chronic use of *C. angustifolia* (141). Moreover, a 42-year-old female presented with epigastric pain, vomiting and intermittent fever after intake of 200 ml of dried senna leaves for 2 years. The patient was diagnosed with portal vein thrombosis (PVT) (142). Another case of subacute cholestatic hepatitis has been reported in 77-year-old male. The patient admitted taking Senna for the treatment of constipation (144). Additionally, chronic use of *C. angustifolia* has been associated with serious conditions like chronic diarrhea and loss of fluid and electrolyte (141). Furthermore, cases of sever hepatic damage associated with Senna are rare. The hepatotoxic effect of Senna can be ascribed to its major constituent, sennosides, which are present in leaves and fruits. Sennosides split to rhein anthron that resemble hepatotoxic danthron (93,141,143). Anthraquinone glycosides also present in senna, which are suspected to cause hepatic diseases as well (100,143).

Pennyroyal oil:

Pennyroyal oil, which is also known as squawmint oil, is derived from two plant species

Hedeoma pulegoides and *Mentha pulegium* (100,145). It has a mint-like odor and it has been used as insect repellent and abortifacient since Roman times (146,147). Pennyroyal oil has been used as a treatment for cold, menstruation and to purify blood (148,149). Additionally, it has been used as a therapy for upper respiratory tract and ear infections (149). However, sever cases of hepatotoxicity associated with pennyroyal oil ingestion have been reported (150). A small amount of oil (10-15 ml) can cause sever toxicity like liver and lung damage and can cause death as well (148,149). The primary constituent of pennyroyal oil is pulegone and it contains some other monoterpenes such as neomenthone, menthone and iso-menthone (149).

Accordingly, one case of pennyroyal oil toxicity involved an 8 week-old boy who drank around 120 ml of tea made from mint plant that contains toxic pennyroyal oil. The infant had fulminant liver failure with cerebral edema caused by menthofuran constituent of pennyroyal oil. He died shortly after initial symptoms appeared (150). Another case involved a 6 month-old boy who took aspirin and 90 ml of tea (3 times per week) from home grown mint plant for his congestion and colic. The baby had hepatic dysfunction with sever epileptic encephalopathy. The plant found to contain both menthofuran and pulegone (150). Additionally, 24 year-old women took both pennyroyal extract and black cohosh root for induction of abortion. She continued taking pennyroyal and black cohosh with unknown amount and she died (149). Anderson et al (149) reported two cases of pennyroyal oil toxicity in two women who drank a preparation of pennyroyal tea to induce menses. The first woman developed dizziness and weakness after ingestion of tea and recovered later. The other woman had mild abdominal cramps; however, she drank more of the tea because the menses did not start and developed sever abdominal cramps and nausea. After 5 days the menses occurred and she recovered. Some studies showed that N-acetylcysteine provides a protection against pennyroyal inducing hepatotoxicity (30,150).

Margosa oil (*Azadirachta indica*):

Margosa oil, yellowish oil with disagreeable taste and smell, is extracted from Neem tree seeds that are native to India (151). Margosa oil or Neem oil is usually given to infants in India, Thailand, Indonesia and Sri Lanka to maintain good health. The oil contains volatile sulphor compounds, fatty acids as well as bitters like nimbin, nimbidin, nimbinin and nimbidol, which are responsible for

its toxicity (151). Accordingly, hepatotoxicity of neem oil resembles Reye's like syndrome, which characterizes by mitochondrial toxicity, microvesicular steatosis and depletion of hepatic ATP and glycogen stores (93). One case of neem poisoning that resembles Reye's syndrome has been reported in an infant. The liver biopsy of this infant showed fatty infiltration of liver, proximal renal tubules and cerebral edema (152). Two cases of encephalopathy caused by margosa oil poisoning in infants have been reported (151). A 5-month-old boy given 5 ml of oil after drinking milk presented with generalized convulsions and loss of consciousness. The second patient was a 3-month-old girl who had few drops of oil presented with generalized convulsions. Both babies recovered. Furthermore, Simiaf et al (152,153) reported Reye-like syndrome due to intake of Margosa oil in 13 infants and children. Another case of Neem oil poisoning involved a 5-year-old boy who developed a neurodeficit due to accidental intake of Margosa oil (154). Moreover, Neem oil reported to cause renal tubular acidosis in 51-year-old man after consumption of large amount of oil (155). The patient was also diagnosed with hepatotoxicity, anemia, encephalopathy and coagulopathy.

St. John's Wort (*Hypericum perforatum*):

Hypericum perforatum is an herbaceous perennial herb that is indigenous to Europe (156). The aerial part of this herb is used for the preparation of St. John's Wort (SJW) extract that has been traditionally used for more than 200 years as a remedy for wide spectrum of medical illnesses such as insomnia, bronchitis, burns, gastritis, hypothyroidism, insect and snake bites, scabies and cancer (156,157,158). Mainly, SJW has been used as an anti-depressant remedy and became one of the top selling anti-depressant agents (156,158). *H. perforatum* has been known to interact with numbers of drugs, which can be beneficial like increasing response of clopidogrel and reducing toxicity of irinotecan (159). However, SJW raised concerns regarding its life-threatening interaction with other conventional drugs including cardiovascular (Digoxin), oral contraceptives, immunosuppressants (Cyclosporin), chemotherapeutics (Irinotecan), anti-depressants (Amitriptyline), anti-diabetics (Gliclazide), anti-androgenics (Finasteride), anti-retrovirals (Indinavir), benzodiazepines and statins (111,158,159,160). Particularly, these drugs are substrates of either cytochrome P450 or P-glycoprotein (156). Moreover, interactions of SJW with other drugs reported to cause sever

consequences involving the reduction of blood cyclosporine levels, reduction of plasma levels of anticancer and antiretroviral drugs, causing serotonin syndrome or unwanted pregnancies (156,159). One case involved a 59-year-old male who presented with hyperlipidemia and initially took pravastatin (80 mg/day). His medication changed to rosuvartatin (10 mg/day) due to presentation of hypercholesterolemia. He admitted taking SJW (300 mg twice/day) as a remedy for insomnia. Accordingly, the total levels of cholesterol and low-density lipoprotein cholesterol level were markedly increased due to SJW-rosuvartatin interaction (161). Additionally, a 29-year-old female underwent cadaveric kidney and pancreas transplant and had been on cyclosporine (100 mg) twice a day as well as *H. perforatum* extract (300 mg) twice a day for up to 8 weeks. The patient presented with reduced plasma cyclosporine concentrations due to interaction between SJW and cyclosporine drug (162). Another case of SJW-drug interaction is presented in a 36-year-old patient who received a liver transplant due to cirrhosis. The patient took a cyclosporine drug (175 mg) twice a day with *H. perforatum* tablets (900 mg) twice a day as an anti-depressant. The patient developed severe acute rejection as well as reduction of cyclosporine level (163). Another case of SJW-drug interaction has been reported in a 41-year-old female diagnosed with disorganized schizophrenia. She took clozapine (500 mg/day) for 6 months accompanied with SJW extract (300 mg three times/day). The clozapine plasma concentration was reduced and disorganization was increased in the patient due to SJW-clozapine interaction (164). Moreover, SJW consists of several pharmacological active constituents but the main ingredient is hyperforin, which is suspected to cause SJW-drug interaction (156,157). Another important ingredient of SJW is hypericin, which can cause some of herb-drug interaction events (159). Moreover, Hyperforin showed to interact with many neurotransmitters such as serotonin, dopamine, gammaaminobutyric acid, glutamate and noradrenaline (156).

Valerian (*Valeriana officinalis*):

Valeriana officinalis is a plant (Valerianaceae family) that is indigenous to North America, Europe and Asia (165). The dried root of *V. officinalis* is known as valerian, which has been used for long time by ancient Rome and Greece as sedative and anti anxiety remedy and for treating insomnia (165,166). Additionally, it has been used as a remedy for treating palpitation,

headache, gastrointestinal pain, high blood pressure, sleeping disorders and menstrual cramps (166). Valerian is a common herb and found in many over the counter preparation either alone or combined with other herbs (167). Some hepatotoxic events associated with valerian ingestion have been reported. The first cases of valerian-induced hepatotoxicity were reported in 1989, where 4 patients took over the counter sleep aids containing valerian (168). Another case of valerian hepatotoxicity was described in a 27-year-old female took 1 capsule of valerian root extract for 3 months and developed hepatic inflammation. She recovered after discontinuation of herbal preparation (165). Moreover, valerian showed to have an interaction ability with other botanicals and can cause a sever injuries (169). Accordingly, a 43-year-old woman who ingested valerian with skullcap and black cohosh and some other herbal preparations developed hepatitis (14). MacGregor et al. (168) described four cases of herb-herb interaction causing hepatic injury. Four women aged between 41 and 57 developed acute hepatitis after consumption of two herbal medications (Kalms and Neurelax) for stress relief. Later studies showed that Kalms contains valerian and skullcap as well as some other herbs where Neurelax contains skullcap only.

Mistletoe (*Viscum album*):

Mistletoe is a woody perennial plant that belongs to Loranthaceae family and grows on oaks and other trees (170). It is native to Asia, Europe and England (170,171). Some synonyms of mistletoe are all-heal, bird lime mistletoe, bird lime, European mistletoe, and viscum (170). Helixor, Iscucin, Iscador and Plenosol are trade names of mistletoe (171). All mistletoe parts have been widely used as a treatment for several conditions including hypertension, headache, insomnia, epilepsy, asthma, infertility, cancer and urinary disorders (30,171). Accordingly, mistletoe found to have potential toxic constituents including β -phenylethylamine, acetylcholine, tyramine and propionylcholine (172). It also contains lectins and viscotoxin that cause several side effects such as hypertension, chills and fever (170). The hepatotoxicity related to mistletoe consumption is rare and only few cases have been reported (111). One case report involved a 49-year-old woman presented with general malaise, nausea and dull ache in the right hypochondrium. She admitted taking herbal medication containing Mistletoe, skullcap, motherwort and kelp for her nervous tension and she developed acute hepatitis (172).

Skullcap (*Scutellaria baicalensis*):

Scutellaria baicalensis is an herbaceous herb that belongs to mint family and has two species. The first species is *S. baicalensis* that is alternatively known as Chinese skullcap, Baikal skullcap or Huang-qin and commonly used in Chinese medicine. The second species is *S. lateriflora* that also known as blue skullcap, hoodwort or Virginian skullcap that is native to Americans (173,174). *Scutellaria* has been used as a sedative and anti-inflammatory agents (106) and for treating several ailments like cancer, jaundice, hepatitis, anxiety, nervous tension, hysteria and epilepsy (168,175,176). Both species includes terpenoid compounds, which can cause hepatotoxic effects (111). Several case reports of hepatotoxicity after skullcap ingestion either alone or in combination with other botanicals have been reported (173). One case report of 28-year-old man developed fulminant hepatic failure with multiple sclerosis after congestion of skullcap (6 tablets/ day) with pau d' arco and Zinc. The patient required liver transplantation and died shortly after the liver transplant. He was diagnosed with veno-occlusive disease and fatal hepatic failure due to contamination of herbs with toxic plants (176). Another case involved a 78-year-old woman who took one herbal supplement called "Move Free Advanced" with multivitamins daily for treating arthritis. The woman presented with significant cholestasis and hepatitis; however, she improved after discontinuation of herbal medicine. Move Free Advanced supplement found to contain Chinese skullcap and black catecho (173). Another case of skullcap hepatotoxicity included a 77-year-old female who presented with weight loss, anorexia and tiredness. The patient consumed 6 units of alcohol per week. She was diagnosed with hepatitis with pulmonary complication. Later, she admitted taking three herbal preparations, which are BFC (for wasting diseases), Nervine (for anxiety) and Bowel tonic (for peristalsis) three times per day for 6 month. Further investigation reported the presence of skullcap and comfrey in BFC, which caused hepatic injury and pulmonary lesions in the patient (177). Other case reports of hepatotoxicity due to interaction of skullcap with other botanical were mentioned earlier (14,168,172).

Noni juice (*Morinda citrifolia*):

Noni juice is derived from Polynesian tropical fruit of *Morinda citrifolia* tree and it is commonly used in European tabloid press (100). Fruit, roots and leaves of *M. citrifolia* has been used for more

than 2000 years as a herbal remedy and wellness drink (178,179,180). Additionally, it has been used for treating many health problems including cancer, AIDS, elevated blood pressure and mental depression (178,181). However, noni juice has been associated with several hepatotoxicity events. The potential toxic constituent of *M. citrifolia* is anthraquinones like morindone, nordamnacanthal, rubiadin, rubiadin-1-methyl ether, anthraquinone glycoside, which are known for their hepatotoxic potential (180,182). According to Stadlbauer et al. (180), a 29-year-old man who previously had acute hepatitis due to paracetamol developed sub acute hepatic failure after consumption of 1.5 L of noni juice for more than 3 weeks. The patient required a liver transplantation. Moreover, a 62-year-old woman who drank 2 L of noni juice developed acute hepatitis and recovered after cessation of herbal drink (180). Another case of toxicity associated with noni juice involved a 45-year-old man who had a glass of noni juice daily for few weeks for prophylactic reason. He developed an acute hepatitis and recovered after withdrawal of herbal drink (178). Fulminant hepatitis was reported in 24-year-old female after consumption of noni juice for stimulation of her immune system (182). The patient recovered after discontinuation of the noni drink. Moreover, a 14-year-old-boy drank approximately 600 ml of an antioxidant drink to improve energy and developed acute hepatitis. The drink contains several ingredients including noni berries (91 mg/kg). However, the boy's health improved (183).

***Amanita phalloides*:**

One of serious species that causes severe mushroom poisoning is *Amanita*, mostly *A. phalloides* or death cap (94,184). There are two diverse groups of toxins found in *Amanita*. The first toxin is phalloidin, which affects enterocytes cellular membrane (184). The second toxin is amanitins mainly α - amanitin, which is absorbed in gastrointestinal tract and can affect liver (184). The later is also responsible for the damage of kidney, pancreas, brain, testes and hematopoietic system. Additionally, death can be resulted from α - amanitin poisoning (94). One case of fulminant hepatic failure after ingestion of *A. phalloides* was reported. A 64-year-old woman presented with vomiting, abdominal pain, diarrhea and nausea after consumption of wild mushroom (2 bowl) from her backyard. The patient was diagnosed with fulminant liver failure and required liver transplantation. In this case, the wild mushroom (*A. phalloides*) found to contain α - amanitin that

induced hepatotoxicity (185). Another case of *A. phalloides* poisoning involved a 16-year-old female who presented with vomiting, abdominal pain, diarrhea and nausea. She had wild mushroom and diagnosed with liver failure and required liver transplantation (186). Moreover, four cases of *A. phalloides* poisoning have been reported in children (187). One case involved a 2.5-year-old female presented with diarrhea and vomiting after ingestion of two mushrooms picked by her mother from the woods. The girl had elevated liver enzymes and died due to massive hepatocellular necrosis as well as macrovesicular steatosis. The second case involved an 8-year-old male presented with abdominal pain and nausea after eating fried mushroom. He had elevated liver enzymes and developed renal failure and died due to multiple organ failure. The third case involved an 11-year-old boy who ate fried mushroom collected by his mother from forest and presented with vomiting, nausea and diarrhea. All his family ate from the same mushroom on their breakfast. They all had high liver function tests. The mother died but other family members recovered after treatment including the 11-year-old boy. The last case involved a 10-year-old male presented with vomiting and developed hepatic encephalopathy after eating mushroom that he picked. His condition worsened and required an orthotopic liver transplantation due to development of fulminant liver failure. However, the boy recovered after transplantation. In all four cases, *A. phalloides* mushroom found to be responsible for mushroom poisoning (187). Moreover, a 72-year-old female and her 45-year-old son presented with diarrhea, vomiting and abdominal pain after consumption of wild mushroom picked by themselves. They both had elevated liver enzymes and diagnosed with *A. phalloides* poisoning. They recovered after receiving treatment (188).

***Sassafras (Sassafras albidum)*:**

Sassafras albidum is an aromatic tree, which is native to Eastern North America (189). Sassafras oil that obtained from both root and root bark has been used as flavoring and sudorific agent as well as treatment for insect bites and stings (189). It also used as a therapy of inflammation of eyes, urinary tract conditions and kidney diseases (145,189). The main active constituent of Sassafras oil is safrol (80%), which is also present in nutmeg, cinnamon, black pepper and mace (145,190). Moreover, it has been found that a small amount of sassafras oil can be toxic to human (191). In 1949, the consumption of large

quantity of sassafras oil reported to cause neurological effects like hallucinogenic and psychoactive effects (192). In 1960, the FDA banned the use of this oil due to high safrole levels (145). Accordingly, sassafras oil has been classified as a hepatocarcinogen of low grade (192). One case of death in a man who consumed sassafras oil (1 teaspoonful) has been reported (190). The patient used synthetic form of the oil and presented with vomiting, collapse and stupor then died. Additionally, five cases of children aged between 1 and 2.5 years old reported consumption of sassafras oil and presented with several symptoms. All children were vomiting, two were stupor, one had aphasic symptom, one presented with shock sign and three had vertigo signs (190).

Echinacea:

Echinacea consists of three species that has been used medicinally including *E. angustifolia*, *E. pallida* and *E. purpurea* (158,193,194). It is a perennial herb that is native to North America and commonly known as purple coneflower (194,195). Other synonyms include black Sampson, black susan, hedgehog, indian head, comb flower and Missouri snake root (136). *Echinacea* has been used by Plains Indians as a remedy for respiratory infection and fever (194). It also has been used as immune booster and as a therapy of common cold (169,195). Accordingly, *Echinacea* contains pyrrolizidine alkaloids (PA), which explains the hepatotoxicity associated with it (196). One case of *Echinacea* hepatotoxicity involved a 45-year-old man who diagnosed with acute cholestatic autoimmune hepatitis due to intake of *Echinacea* (197). However, no significant hepatotoxicity of *Echinacea* has been reported. The potential hepatotoxic effect of *Echinacea* is when taken for more than 8 weeks and with other known hepatotoxic drugs like amiodarone, anabolic steroids, ketoconazole or methotrexate (193,194). Furthermore, there are other known Pyrrolizidine alkaloids-containing herbs that have been associated with hepatic injury as well as death including *Heliotropium*, *Senecio* and *Crotalaria* (10,93,94,198,199). These herbs are common in Africa and Jamaica where intoxication with PA is accidental due to contaminated food (30). In 1992 and 1993, around 4000 individuals had abdominal pain, ascites, alteration of consciousness and hepatomegaly after consumption of grain contaminated with *Heliotropium lasiocarpum* (200). Additionally, four women were diagnosed with VOD after intake of herbal tea containing

Heliotropium lasiocarpum in China (201). *Senecio* species like *S. burchelli* and *S. ilicifolius* have been associated with several hepatic diseases (94,199,202). A 5-day-old female infant diagnosed with fatal hepatic VOD (199). The mother used to drink herbal tea daily during her pregnancy with consumption of cannabis and hallucinogenic mushroom. The herbal tea found to contain PA and senecionine. Another case of *Senecio* intoxication reported in Arizona where two infants diagnosed with VOD (94). Accordingly, several cases of *Senecio* poisoning have been reported (202). The patients were presented with nausea, vomiting, abdominal pain, accumulation of ascitic fluid and hepatomegaly, which are features of Chiari's syndrome. Moreover, *Crotalaria* species reported to cause hepatic damage as well (203). In Jamaica, children were diagnosed with hepatomegaly, ascites and cirrhosis after intake of bush tea as a therapy for acute illness. Bush tea found to contain *Crotalaria* and *Senecio* (30).

DISCUSSION

Herbal medicines have been used for centuries and their usage continues to rise worldwide due to the perception that natural products from plants are safer than usual drugs and free of side effects (5). However, severe liver injury has been observed following the consumption of several plant preparations (204). Hence, the liver is the major target of injuries induced by drugs because it is the main organ of drug metabolisms, where foreign chemicals are transformed by metabolizing enzymes including mixed-function monooxygenases, microsomal cytochrome P450 enzymes, UDP-glucuronosyltransferases, sulfotransferases, and glutathione-S-transferases (205). Moreover, botanical-induced hepatotoxicity and liver abnormalities have been extensively documented. Many herbal remedies have been recognized as toxins that cause mild or severe liver damage and some have fatal outcomes (204). In this review, we listed cases of adverse hepatic effects associated with the use of natural medicine and the potential risk of some herbs.

Actea racemosa or *Cimicifuga racemosa*, which is commonly known as black cohosh, has been widely used as a common treatment of symptoms of menopause among women. It has also been reported to be safe and to improve menopausal symptoms (204-207). Although several studies demonstrated the efficacy of black cohosh as a therapy (208-211), hepatotoxicity

associated with black cohosh ingestion was reported (205). The concerns regarding the safety of cimicifuga is due to the composition of this plant, which consists of both hepatoprotective and hepatotoxic components (1,14,212,213). Moreover, previous reports have been associated black cohosh with fulminant liver failure (24), autoimmune hepatitis (25), and acute hepatitis (14). Accordingly, the main mechanism of injury of black cohosh is unknown. However, the hepatotoxicity could be attributed to the triterpene glycoside, the major constituent of black cohosh, as well as an immunoallergic mechanism due to presence of tissue eosinophilia (106,113). Another potentially hepatotoxic plant is *Larrea tridentate*, or chaparral bush, that has been widely used for treating variety of conditions include snakebite, bronchitis and rheumatic pain (15,29). On the other hand, many cases have been reported as a proof of causal relationship of chaparral and hepatotoxicity (15,32,214-218). Accordingly, liver injury associated with chaparral consumption includes acute hepatitis (31,216,214), hepatic fibrosis (31), and hepatic necrosis (32). Some studies linked chaparral toxicity with duration of use as toxicity increases with long duration (219). Additional to hepatotoxicity, chaparral ingestions have been associated with dermatologic and renal toxicity as well (15). The mechanism of action of chaparral toxicity remains unknown (93). However, it could be attributed to its active constituent, nordihydroguaiaretic acid (NDGA), which causes inhibition of lipoxygenase or cyclooxygenase pathways (220), inhibition of cytochrome p450 (221) and chaparral estrogen activity (219). Saw palmetto, the active ingredient in *Serenoa repens*, is an American dwarf palm tree that is widely used for BPH (222). Since 1800s, the berries of this plant have been known for their medicinal importance to treat patients with prostatic enlargement (223). Some mild side effects have been associated with *S. repens* such as headache, abdominal pain, and nausea (35). Additionally, saw palmetto was found to be hepatotoxic and harboring severe side effects including acute liver damage (41), cholestatic hepatitis (113) and acute pancreatitis (16,36,224). According to Hamid, Rojter & Vierling (39), prostata is a common preparation of saw palmetto that has been implicated in protracted cholestatic hepatitis. The mechanism by which saw palmetto induces its effect is not fully understood (36), however; some suggestions are pointing to the estrogenic and antiandrogenic effects (36). Pyrrolizidine alkaloids-containing herbs have been used as herbal remedies to treat many

illnesses. One of well-known pyrrolizidine alkaloids-containing agent is *Symphytum officinale* that is commonly known as comfrey (8,54). Leaves and roots of comfrey have been used as a remedy externally (bone fractures, reduce joint inflammation, wound healing) and internally (gastroduodenal ulcers and gastritis) (8,46). However, pyrrolizidine alkaloids, which were first recognized as toxins in 1920 (225), are major health hazards (8). Comfrey has been reported to be hepatotoxic and cause hepatic VOD (8). VOD of the liver has been linked with ingestion of contaminated plants with pyrrolizidine alkaloids (54). Moreover, some other factors that contribute to VOD of the liver include chemotherapy, irradiation, tyrosinaemia and systemic lupus erythromatosus (54). The mechanism of action of comfrey has not been established due to the involvement of multiple constituents (226). Hepatotoxicity of comfrey could be linked to several factors including susceptibility of host, route of exposure as well as ingested dose (43,51). Though, comfrey-induced injury could be due to destruction of veins that cause cirrhosis and finally liver failure (226) or hepatic congestion due to fibrous obliteration of small hepatic veins (54). Another serious drug-induced hepatotoxicity is constituted by *Teucrium* genus, which involves over 300 species worldwide (60). Two important species are *Teucrium chamaedrys* (wall germander) and *Teucrium polium* (60,17) that have been used for more than 2000 years as a treatment against overweight and obesity (17). Although, germander has been considered to be risk free, many cases of its hepatotoxic effect have been reported indeed (5,17,60,65). *Teucrium polium*-induced hepatotoxicity has been observed in several cases as well (61,64,227-230). The mechanism of hepatotoxic action of germander is not well known. However, some studies may contribute to the hepatotoxic potential pointing to the furano neoclerodane diterpenoids constituent, found mainly in teucrin A (61,231). Accordingly, two cases reported that dual mechanisms- direct toxicity and secondary immune reactions- can mediate germander hepatotoxicity (60,232). Moreover, an immunoallergic mechanism may be involved and accounts for germander toxicity (17). Kava, obtained from *Piper methysticum* roots, has been traditionally used for ceremonial and medicinal purposes and as remedy for insomnia and anxiety (68). The active constituent of kava is kavapyrones, which are responsible for the pharmacological properties (68,70,73). However, the first case report described the

hepatotoxic effect of kava was in 1998 (233). Consecutively, several case reports of association of kava consumption with hepatic injury have been reported (70,234). The spectrum of liver injury induced by kava ingestion includes hepatitis, cirrhosis, and liver failure (68). Yet, the mechanism involved in kava hepatotoxicity has not been identified, however, immunoallergic reaction and metabolic idiosyncratic reaction have been proposed (70,235). Various risk factors may contribute to liver toxicity of kava including genetic polymorphism of cytochrome P450 enzyme, co-medication, and existing liver injury (236). Moreover, *Chelidonium majus* or greater celandine is a well-known herbal remedy for the treatment of gastrointestinal tract diseases (81). However, Greater Celandine showed to cause several hepatotoxic events. The toxic constituent of greater celandine responsible of hepatotoxicity is not yet known (136). Moreover, the exact mechanism of liver toxicity is unknown. Some of suggested mechanisms include an autoimmune mechanism due to the presence of eosinophilic infiltrates and autoantibodies in some cases. Another possible mechanism is idiosyncratic mechanism (13). Another dangerous herbaceous botanical is *Atractylis gummifera*, which has been commonly used in Mediterranean countries as antipyretic, purgative and diuretic (30,100). This plant is a life-threatening poisoning where all plant parts are toxic (240). Moreover, *A. gummifera* has been associated with several cases of hepatotoxicity including hepato-renal injury (89), hepatic necrosis (91) and death (91,95). Moreover, two main constituents are responsible for *A. gummifera* toxicity, which are atractylosides and gummiferin. The proposed mechanism of *A. gummifera*-induce hepatotoxicity could be due to mitochondrial toxicity via inhibition of oxidative phosphorylation and induction of oxidative stress (95,100). *Callilepis laureola* or Impila is another dangerous herb (97). It is a multifunctional remedy that used for treating stomach discomfort, cough, worm infection and impotence (97,98). However, Impila is a sever poison and patients poisoned by it show sever hypoglycemia (102). Moreover, several reports reported cases of hepatotoxicity and renal toxicity including acute renal failure (241), hepatocellular necrosis (98) and hepatic and renal dysfunction along with hypoglycemia (102) as well as death (99). As in *Atractylis gummifera*, *Callilepis laureola* contains toxic atractylosides, which is responsible for fulminant hepatitis and renal tubular necrosis injury (101). Additionally, atractylosides act by

inhibiting the oxidative phosphorylation (242). Chinese Herbal Medicine has been known for more than 4000 years and used as therapy for several illnesses (103). However, various hepatotoxic effects after consumption of Chinese herbal preparations have been reported (94). Jin Bu Huang is a common Chinese herb that used as analgesic, sedative and sleeping aid (30). However, JBH has been associated with acute and chronic hepatitis (105,107). Accordingly, the active component of JHB is the extract from *Lycopodium serratum* plant (94,106). The potential mechanism of liver damage induced by Jin Bu Huang is unknown (243). Additionally, Ma Huang derived from *Ephedra sinica* has been commonly used in China as a slimming aid as well as a therapy for cough and bronchitis (109,110,111). Several cases of Ma Huang hepatotoxicity have been reported (109,110,115,116). The major constituent in Ma Huang that is responsible for toxic effects is Ephedrine (110). The hepatotoxic action of Ma Huang could be immune-mediated (106,130,244). Another commonly used herb in China is Shou-Wu-Pian, which is derived from *Polygonum multiflorum* (113,119). It is a mixture of Chinese herbs that has been used as a treatment for several illnesses including backache, constipation, dizziness, greying of hair, spermatorrhea, lumbago and treating symptoms of chronic prostatitis (120,121,122). Yet, Shou-Wu-Pian found to cause acute hepatitis in adults and children (119,120,125). This hepatotoxic effect of The Shou-Wu-Pian is ascribed to toxic constituent, anthraquinone (120). Furthermore, the potential hepatotoxic mechanism of Shou-Wu-Pian is not fully described (125). Another Chinese herb is *Dictamnus dasycarpus*, which has been used for treating skin diseases (127). Few reports reported hepatotoxic events and death associated with consumption *D. dasycarpus* with other herbal preparation (128,129,130,131). Additionally, Kampo medicine including Dai-Saiko-to and Syo-saiko-to consists of mixture of herbs that has been used as a remedy of several illnesses like dyspepsia and pyretic diseases (10,133). However, these herbal medicine have been linked with some cases of hepatotoxicity (132,134). Accordingly, the toxic agents responsible for hepatotoxicity of these kampo herbs are glycyrrhiza, and scutellaria constituents (132,133). Moreover, the mechanism by which these herbs induce hepatotoxicity is not fully understood (132). Another popular plant is Kombusha mushroom, which is not a true mushroom as it involves symbiotic yeast and

bacteria grouped together and surrounded by a permeable membrane (132). It is commonly used as health tonic to improve health (106). Nevertheless, several cases of toxicity have been reported due to intake of Kombusha tea (138). The potential mechanism involved in Kombusha toxicity could be attributed to usnic acid found in Kombusha. Thus, usnic acid can cause hepatic damage due to uncoupling of oxidative phosphorylation of mitochondria and induction of oxidative stress (106,113). Moreover, toxic action of Kombusha could be due to contamination if it is prepared in ceramic of lead containers (139,140). *Cassia angustifolia* or senna is another common herb that has been used for its laxative properties (141,142). The leaves and fruits of senna have been associated with toxic hepatitis (143), acute hepatic failure (141), portal vein thrombosis (142) and subacute cholestatic hepatitis (144). The toxic constituent of senna is sennosides and anthraquinone glycosides (93,94,100,143). Moreover, the hepatotoxic effect of *C. angustifolia* is uncommon and could be due to exposure of liver to massive amounts of toxic metabolites of anthraquinone glycosides (141,142). Moreover, Pennyroyal oil obtained from *Mentha pulegium* or *Hedeoma Pulegoides* has been used as abortifacient and pesticide against insects and fleas (145,146,149). However, several cases of pennyroyal oil intoxication have been reported (150) as well as cases of fulminant hepatic necrosis (149). The main constituent responsible of pennyroyal hepatotoxicity is pulegone and some other monoterpenes (149). The possible mechanism of pennyroyal causing hepatotoxicity involves the oxidization of menthofuran, which is pulegone metabolite, by cytochrome P450s (245,246). Moreover, the pulegone cause depletion of hepatic glutathione through formation of electrophilic metabolites, which increases the concentration of menthofuran leading to hepatotoxicity (149,247). Another common oil is Margosa or Neem oil extracted from *Azadirachta indica* A. Juss (Neem tree), which has been widely used to obtain good health and it is usually given to infants and children (151). However, several cases of hepatotoxicity, neurodeficit and renal tubular acidosis associated with Margosa poisoning have been reported (151,152,154,155). The toxic effect of Margosa oil has been attributed to the bitters constituents of this oil including nimbin, nimbidin, nimbinin and nimbidol (152). Accordingly, the potential mechanism of toxicity of Margosa oil could be due to toxic effect on mitochondria (155). One of most important herb involved in herb-drug

interaction is St. John's Wort (SJW) extracted from *Hypericum perforatum* (165). More than 2000 years ago, SJW has been used as a remedy for several conditions but mainly as an anti-depressant (156,157,158). It has been implicated in interaction with various pharmaceutical (111,158,159,160). SJW-drug interaction can lead to serious consequences for example causing intermenstrual bleeding when taking with oral contraceptives, increasing total cholesterol levels and LDL cholesterol levels when taking with rosuvartatin, reducing plasma cyclosporine concentrations, acute liver transplant rejection when taking with cyclosporine (161,162,163,248). The responsible constituent of causing SJW-drug interaction is known to be hyperforin (156,157). Hyperforin causes induction cytochrome P450 enzymes level, particularly CYP3A4 and induction of P-glycoprotein activity (249). Another hepatotoxic plant is *Valeriana officinalis* or valerian that is available as a mixture with other herbs as over the counter medicine for the treatment of anxiety and insomnia (167). However, valerian has been associated with both cytotoxicity (250) and hepatotoxicity (168) with only few cases have been reported (251). Additionally, valerian has the ability to interact with other drugs and herbs (169). The main constituents of valerian are valepotriates (iridoids) and volatile oil with some other alkaloids (252). Moreover, alkylating agents found to be responsible for the toxic effects of valerian (168). The exact mechanism of valerian causing hepatotoxicity is unknown (166). However, one of suspected mechanism of toxicity involves hypersensitivity reactions (10). Furthermore, *Viscum album* or European mistletoe is a semi-parasitic woody perennial plant that is indigenous to Europe and Asia (170). The leaves, berries and branches of mistletoe are used for treatment of different conditions like hypertension, asthma, infertility, insomnia, epilepsy, cancer and urinary disorders (30,171). However, mistletoe found to contain toxic constituents in all plant parts like lectins (170). Some of side effects associated with this botanical involve fever, chills and headaches (170). Moreover, mistletoe hepatotoxicity is debated and only few cases have been reported (93,100,168). The possible mechanism of mistletoe-induced hepatotoxicity is unknown and no suggested mechanisms were found. Another commonly used herb is *Scutelloria baicalensis* or skullcap, which has been used as an anti-inflammatory, anti-spasmodic and sedative agent and for treating arthritis, jaundice, cancer, hepatitis, epilepsy and

nervous tension (82,111,173,175,176). However, several reports reported cases of skullcap inducing hepatotoxic injury either alone or in compensation with other herbs such as mistletoe (172,173,176). Accordingly, skullcap contains terpenoid compounds, which are hydrocarbons that consists of isoprene unites. They are widely distributed in nature, particularly in plant kingdom as a constituent of essential oils in oxygenated derivatives form (10,113). The presence of terpenoid compounds in skullcap is a potential mechanism by which skullcap could cause hepatotoxic injury as well as veno-occlusive disease (106). Moreover, NONI juice from *Morinda citrifolia* fruit has been used for centuries as a Polynesian herbal medicine to maintain wellness (180,183). However, the consumption of noni juice has been associated with sever cases of hepatotoxicity including acute hepatitis (178,180,183), fulminant hepatitis (182) and hyperkalemia in a patient with renal failure (253). The main toxic constituents of noni juice are anthraquinones involving rubiadin, rubiadin-1-methyl ether, anthraquinone glycoside, moridone and nordamcanthal that are known to cause hepatotoxic events (180,182). The exact mechanism of noni juice-inducing hepatotoxicity is unknown; however, potential hepatotoxicity could be attributed to the presence of anthraquinones (180). Rhein- a product of anthraquinone- cause intracellular glutathione depletion, mitochondrial membrane potential reduction, lipid peroxidation initiation leading to death of cell by production of oxygen derived free radicals through redox cycling (254). Amatoxin-containing mushrooms like *Amanita phalloides* can cause sever poisoning leading to death (94). Several cases of *Amanita phalloides* poisoning have been reported (185,186,188). Thus, the toxicity is due to two toxins, which are phalloidin and α - amanitin. phalloidin is not sever toxin as it disrupts cellular membrane by irreversible polymerization of both G- and F-actin. Thus, phalloidin is only responsible for gastrointestinal symptoms (184,187). On the other hand, amanitins (α - amanitin) is the one responsible for sever toxicity of *Amanita phalloides*. It is absorbed in intestine affect liver (184). Amanitins causes toxicity by inhibiting the activity of RNA polymerase II leading to interruption of protein synthesis and causing cell death (184,187). Additionally, Sassafras oil extracted from *sassafras albidum* tree has been used as a remedy for several illnesses including urinary tract disorder and kidney diseases (145). However, sassafras showed to contain toxic saffrole as its

major constituent (192). Due to high concentration of saffrole presented in sassafras, FDA banned intake of sassafras (145). Another hepatotoxic herb is *Echinacea* that belongs to North America and has been used by Plains Indians for treating respiratory infections and fever (194,195). Three species have been medicinally used including *E. angustifolia*, *E. pallida* and *E. purpurea*. However, the potential hepatotoxicity of *Echinacea* is linked with prolong intake of herb for more than 8 weeks as well as consumption of other hepatotoxic medications (193,194). Moreover, presence of PA could be associated with liver toxicity but it was reported that PA of *Echinacea* is lacking 1,2 saturated necrine ring associated with toxic effect of PA (193,194). Additionally, the exact mechanism of *Echinacea* hepatotoxicity is not yet determined (193).

We reviewed and analyzed some of herbal preparations and their hepatotoxic effects; however, our review is limited due to some incomplete information regarding dosage of drug, duration of use, ingredients of plant and previous medical history of patients. Additionally, articles were restricted to English only and human studies/cases that occurred during 1900 to 2013 periods.

In conclusion, adverse serious events of hepatotoxicity were reported and evidence provides that herbs are not hepatotoxicity free. Botanicals are self-prescribed and widely available, which make them difficult to control. In order to minimize the harm of herbal products, patients should provide accurate information about their health and susceptibility to liver disease as well as complete details of their usage. Additionally, they should search for herbs that meet good therapy standards and follow recommended dose provided by their physicians or pharmacists. Moreover, healthcare providers and physicians must report about all events associated with herbal use and advise about adverse reactions to such herbs worldwide in a common and accessible web-based database. Extensive education of practitioners, pharmacists and physicians about natural medicines is probably needed and this review intended to pharmacological scientists would be the basis for future seminars and workshops. Further research and studies are required in order to identify toxic constituents in each herbal preparation as well as possible mechanism(s)of hepatotoxicity. We would also suggest that (1) more scientific studies on immortalized normal hepatocytes are needed to identify toxic compounds and understand the

exact mechanism of hepatotoxicity; (2) a database with adverse effects of herbal products should be open and web details should be made accessible to general practitioners; and (3) seminars and workshops on herbal therapy should probably have experts in liver metabolism on board to explain hepatotoxic effects of alternative medicine.

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Table 1. Selected herbs associated with hepatotoxicity

Herbal remedy	Part used	Toxic constituent	Application	Nature of injury	Potential Mechanism of action	Reference
Black cohosh (<i>Actea racemosa/cimicifuga racemosa</i>)	Roots & Rhizomes	Triterpene glycoside	Menopausal symptoms	Hepatic necrosis and bridging fibrosis	Autoimmune, Rare	14,24,25,106
Chaparral (<i>Larrea tridentata</i>)	Leaves	Larrea tridentata (nordihydroguaiar etic acid)	Antioxidant Health tonic	Cholestasis, Chronic hepatitis, cholangitis, cirrhosis	Induction of cytochrome P450 3A Glutathione depletion	15
Prostata (<i>Serenoa repens</i>)	Berries	Saw palmetto	Treatment of benign prostatic hyperplasia (BPH)	Cholestatic hepatitis	Antiandrogenic and estrogenic	35,39
Comfrey (<i>syrrnphytium</i>)	Leaves & Roots	Pyrrrolizidine alkaloids (PA)	Broken bone, wound healing, reduce joint inflammation	Hepatic VOD	Veno-occlusive disease	43,237
Teucrium chamaedrys (Wild germander) & Teucrium polium	Aerial part	Neo-clerodane diterpenoids	Weight reduction	Acute and chronic hepatitis, fibrosis	Cytochrome P450 3A induction Glutathione depletion Autoimmune	5,61
Kava (<i>Piper methysticum</i>)	Roots & Rhizomes	Kava lactones (kavain, dihydrokavain)	Anxiolytic, sleeping aid (anxiety disorders)	Acute and chronic hepatitis, Cholestasis, fulminant hepatic failure	Idiosyncratic factor Immunoallergic factor Poor cytochrome P450 2D6 Cyclooxygenase enzymes inhibition (COX-1 and COX-2) Glutathione depletion	69
Greater celandine (<i>Chelidonium majus</i>)	Aerial parts	Unknown	Gastrointestinal tract disorders	Acute hepatitis Cholestatic hepatitis Fibrosis	Autoimmune	106,136
Atractylis gummifera	Roots	Atractyloside & Carboxy-atractyloside	Antipyretic Diuretic Emetic Purgative Chewing gum	Acute liver failure	Mitochondrial toxicity	90,91,95, 106

<i>Callilepis laureola</i> (Impila)	Roots	atractyloside	Health tonic	Hepatic necrosis Renal tubular necrosis	Oxidative phosphorylation inhibition	101,106,242
Jin Bu Huan (<i>Lycopodium serratum</i>)	Mixture of herbs	<i>Lycopodium serratum</i> extract	Analgesic sedative Sleeping aid	Acute hepatitis Chronic hepatitis Steatosis Fibrosis	Autoimmune	30,106
Ma Huang (<i>Ephedra sinica</i>)	Aerial	Alkaloids	Weight loss	Acute hepatitis	Autoimmune	106,109
Shou-Wu-Pian (<i>Polygonum multiflorum</i>)	Root vines	Anthraquinone	Health tonic Antiaging Hair color	Acute hepatitis Acute liver failure	Autoimmune	106,120,125
<i>Dictamnus dasycarpus</i>	Root bark	Unknown	Skin diseases Cough Jaundice Rheumatism	Acute hepatitis Elevated liver enzymes Death	Unknown	127,128, 129
Dai-Saiko-to or TJ-8	Mixture of herbs	Diterpenoids	Chronic hepatitis Dyspepsia Fever Gallstones	Autoimmune hepatitis	Autoimmune	10,106,132
Syo-saiko-to Xiao-chai-hu-tang da- chai-hu-tang TJ-9	Mixture of herbs	Glycyrrhizin	Pyretic diseases	Fatal hepatic necrosis Hepatic granulomas Microvesicular steatosis	Unknown	113,134
Kombucha “mushroom” Tea	Mushroom	Usnic acid	Wight loss Increasing T-cell count Well-being Antiaging	Acute liver failure Hepatitis Acute renal failure with hyperthermia and lactic acidosis	Cytochrome polymorphism Oxidative stress Mitochondrial toxicity	106,137,139
<i>Cassia angustifolia</i> (senna)	Leaves (pods) and fruits	Anthraquinone Sennosides	Laxative Constipation	Acute hepatitis Acute cholestatic hepatitis Acute liver failure	Unknown	106,141,142
Pennyroyal oil (<i>Hedeoma pulegoides</i> & <i>Mentha pulegium</i>)	Leaves	Pulegone	Abortifacient Upper respiratory tract Ear infection	Fulminant liver failure Hepatic dysfunction with epileptic Encephalopathy	Glutathione depletion Cytochrome P450 induction	106,150
Margosa oil (<i>Azadirachta indica</i>)	Seeds	Bitters constituents	Health tonic	Reye’s syndrome	Unknown	100,106,152

St. John's Wort (<i>Hypericum perforatum</i>)	Aerial	Hyperforin	Anti-depressant	Reduce blood cyclosporine levels Reduce plasma anticancer & antiretroviral drug levels Serotonin syndrome unwanted pregnancies	Cytochrome P450 induction P-glycoprotein induction	156,158,159,249
Valerian (<i>Valeriana officinalis</i>)	Root	Valepotriates	Sedative Anti-anxiety	Hepatitis	Unknown	106,152,165,168
Mistletoe (<i>Viscum album</i>)	All parts	Diterpenoids	Hypertension Insomnia Epilepsy Asthma Infertility Urinary disorders	Acute hepatitis	Unknown	30,171
Skullcap (<i>Scutellaria baicalensis</i>)	-	Terpenoid	Sedative Anti-inflammatory	Veno-occlusive disease Subsequent fatal liver failure Cholestasis Hepatitis	Veno-occlusive disease	106,173,176
Noni juice (<i>Morinda citrifolia</i>)	Fruit Roots & Leaves	Antraquinone	Health tonic	Sub acute hepatic failure Acute hepatitis	Glutathione depletion Mitochondrial membrane potential reduction Lipid peroxidation initiation	106,178,180,254
Amanita phalloides	Mushroom	Phalloidin & α -amanitin	Food	Fulminant liver failure Death	Inhibition of RNA polymerase II	184,185,187
Sassafras (<i>Sassafras albidum</i>)	Root & Root bark	Safrole	Sudorific agent Inflammation of eyes Urinary tract & kidney diseases	Rare in human	Unknown	189
Echinacea <i>E. angustifolia</i> <i>E. pallida</i> <i>E. purpurea</i>	All parts	Pyrolizidine alkaloids (lack 1,2 saturated necrine ring)	Respiratory infection Fever Immune booster	Acute cholestatic autoimmune hepatitis	Unknown	194,195,197