

Review Article

A Review on Hepatotoxicity of Phytomedicines

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ABSTRACT

Herbal hepatotoxicity is increasingly recognized as herbal medicines become more popular in industrialized societies. Some herbal products may potentially benefit people with liver disease; however, these benefits remain generally unproved in humans, and a greater awareness of potential adverse effects is required. Herbal use is often not disclosed, and this may result in a diagnostic delay and perpetuation or exacerbation of liver injury. Female gender may predispose to hepatotoxicity, and concomitant agents that induce cytochrome P450 enzymes may also increase individual susceptibility. The range of liver injury includes minor transaminase elevations, acute and chronic hepatitis, steatosis, cholestasis, zonal or diffuse hepatic necrosis, hepatic fibrosis and cirrhosis, veno-occlusive disease, and acute liver failure requiring transplantation. In addition to the potential for hepatotoxicity, drug-drug interactions between herbal medicines and conventional agents may affect the efficacy and safety of concurrent medical therapy. This review focuses on emerging hepatotoxins and patterns of liver injury, potential risk factors for herbal hepatotoxicity, and herb-drug interactions. Appropriate reporting and regulatory systems to monitor herbal toxicity are required, in conjunction with ongoing scientific evaluation of the potential benefits of phytotherapy.

Key words: herbs, hepato-toxicity, Cytochrome P450, hepatitis.

INTRODUCTION

The liver, hepar, is a vital organ present in vertebrates and some other animals. It has a wide range of functions, including detoxification, protein synthesis, and production of essential biochemicals necessary for digestion. The liver is necessary for survival; there is currently no way to compensate for the absence of liver function in the long term, although new liver dialysis techniques can be used in the short term. This organ plays a major role in metabolism and has a number of functions in the body, including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It lies below the diaphragm in the abdominal-pelvic region of the abdomen. It produces bile, an alkaline compound which aids indigestion via the emulsification of lipids. The liver's highly specialized tissues regulate a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions.

Stores vitamins, sugar and iron to help give your body energy.

Controls the production and removal of cholesterol.

Clears your blood of waste products, drugs, and other poisonous Substances.

Makes clotting factors to stop excessive bleeding after cuts or Injuries.

Produces immune factors and removes bacteria from the bloodstream to combat infection.

Releases a substance called "bile" to help digest food and absorb important nutrients

The classic symptoms of liver damage include the following:

Pale stools occur when stercobilin, a brown pigment, is absent from the stool. Stercobilin is derived from bilirubin metabolites produced in the liver.

Dark urine occurs when bilirubin mixes with urine

Jaundice (yellow skin and/or whites of the eyes) This is where bilirubin deposits in skin, causing an intense itch. Itching is the most common complaint by people who have liver failure. Often this itch cannot be relieved by drugs.

Swelling of the abdomen, ankles and feet occurs because the liver fails to make albumin.

Excessive fatigue occurs from a generalized loss of nutrients, minerals and vitamins.

Bruising and easy bleeding are other features of liver disease. The liver makes substances which help prevent bleeding. When liver damage occurs, these substances are no longer present and severe bleeding can occur.

Various Liver diseases:

Hepatitis: Inflammation of the liver, usually caused by viruses like hepatitis A, B, and C. Hepatitis can have non-infectious causes too, including heavy drinking, drugs, allergic reactions, or obesity.

Cirrhosis: Long-term damage to the liver from any cause can lead to permanent scarring, called cirrhosis. The liver then becomes unable to function well.

Liver cancer: The most common type of liver cancer, hepatocellular carcinoma, almost always occurs after cirrhosis is present.

Liver failure: Liver failure has many causes including infection, genetic diseases, and excessive alcohol.

Ascites: As cirrhosis results, the liver leaks fluid (ascites) into the belly, which becomes distended and heavy.

Gallstones: If a gallstone becomes stuck in the bile duct draining the liver, hepatitis and bile duct infection (cholangitis) can result.

Hemochromatosis: Hemochromatosis allows iron to deposit in the liver, damaging it. The iron also deposits throughout the body, causing multiple other health problems.

Primary sclerosing cholangitis: A rare disease with unknown causes, primary sclerosing cholangitis causes inflammation and scarring in the bile ducts in the liver.

Primary biliary cirrhosis: In this rare disorder, an unclear process slowly destroys the bile ducts in the liver. Permanent liver scarring (cirrhosis) eventually develops.

Herbal Medicines: Herbal Medicine is the use of herbs and medicinal plants as the first medicines is a universal phenomenon. Herbal medicine is a complete holistic system of medicine which uses the healing properties of medicinal plants and involves the use of any or all of the different parts of the plants (roots, leaves, stems and seeds) to treat illnesses. Herbal Medicine is defined as

branch of science in which plant based formulations are used to alleviate the diseases. It is also known as botanical medicine or phytomedicine. The majority of herbal products available today were originated from the same traditional formulas or ingredients. In the early twentieth century herbal medicine was prime healthcare system as antibiotics or analgesics were not available. With increasing use of allopathic system of medicine, herbal medicine gradually lost its popularity among people and it was based on the fast therapeutic actions of synthetic drugs. Almost a century has passed and it has witnessed limitations of allopathic system of medicine. Lately herbal medicine has gained momentum and it is evident from the fact that certain herbal remedies are more effective as compare to synthetic drugs. Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, pain, asthma, and other problems. For example, ephedra is a herb used in Traditional Chinese Medicine for more than two thousand years to treat asthma and other respiratory problems. Ephedrine, the active ingredient in ephedra, is used in the commercial pharmaceutical preparations for the relief of asthma symptoms and other respiratory problem.

Another example of the use of a herbal preparation in modern medicine is the foxglove plant. This herb had been in use since 1775. At present, the powdered leaf of this plant is known as the cardiac stimulant digitalis to the millions of heart patients it keeps alive worldwide.

The World Health Organization (WHO) estimates that 4 billion people, 80% of the world's population, presently use herbal medicine for some aspect of primary health care. The WHO notes that from 119 plant-derived pharmaceutical medicines, about 74% are used in modern medicine in ways that correlated directly with their traditional uses as plant medicines by native cultures. Major pharmaceutical companies are currently

conducting extensive research on plant materials gathered from the rain forests and other places for their potential medicinal value. About 25 percent of today's prescription drugs are at least partially derived from plants.

Reasons for Increasing Use of Herbal Medicine: Several important factors have contributed to the growth of this worldwide phytotherapeutic market, among which the following may be mentioned;

Preference of consumers for natural therapies

Concern regarding undesirable side effects of modern medicines and the belief that herbal drugs are free from side effects, since millions of people all over the world have been using herbal medicines for thousands of years

Great interest in alternative medicines

Preference of populations for preventive medicine due to increasing population ages

The belief that herbal medicines might be of effective benefit in the treatment of certain diseases where conventional therapies and medicines have proven to be inadequate

Tendency towards self-medication

Improvement in quality, proof of efficacy and safety of herbal medicines

High cost of synthetic medicines.

Present scenario of the herbal therapy and Indian herbal market: Traditional Indian practice held that certain drugs should be formulated through the addition of chosen substances that enhances bioavailability of anti-TB drug RIFAMPICIN. Formulation of piperine with rifampicin will save the drug counter effects. Herbal oriented pharmaceutical companies are investing crores of rupees on researching, developing and popularizing OTC remedies. India can be a major player in the global market for herbal product based medicines. Exports of herbal materials and medicines can jump from just Rs. 456 crore in 2000 to Rs.3000 crore in 2005 and with a "grand strategic plan" exports can shoot to Rs.10,000 crore by 2010.

India is sitting on a gold mine of well-recorded and traditionally well-practiced knowledge of herbal medicine. There are very few medicinal herbs of commercial importance, which are not found in this country. India officially recognizes over 3000 plants for their medicinal value. It is generally estimated that over 6000 plants in India are used in traditional, folk and herbal medicine. There are about 9000 firms manufacturing traditional Ayurvedic medicines in India.

Hepatotoxic effects of herbal medicines: Many commonly used herbal medicine in their irregular, high doses or with other medications in long term are toxic. Toxic effects of herbal medicines range from allergic reactions to cardiovascular, hepatic, renal, neurological and dermatologic toxic effects.

Certain herbs have become popular over the last twenty years, but herbal medicine is still poorly understood by the public, medical practitioners and the media. After a brief honeymoon where herbs have been portrayed as "wonder drugs", we are now seeing article after article on the dangers of herbs. As in most situations, the truth lies

hidden under the media hype, bad or poorly understood science, exaggerated claims, and our natural resistance to new ideas. Seeing herbal medicines as either panaceas or as poisons blinds us to the reality that in most cases they are neither. Lack of experience, lack of education, and lack of good information about herbs makes consumers easy victims of marketing exploitation and herbal myths. The same lack of experience, education, and information makes many physicians and other orthodox health care providers suspicious and uncomfortable, especially with the exaggerated claims, miracle cures, and unproven remedies their patients are taking.

We as a culture are coming out of what I call the "Herbal Dark Ages", a period of time when the use of herbs virtually ceased to exist within the United States. A few ethnic communities continued to utilize herbs, but from the 1920's into the 1970's the only herbs that mainstream Americans used were spices in cooking. Out of this almost total lack of exposure we have seen an amazing resurgence of interest in "natural" remedies.

Along with this new interest is a profound ignorance, with many people equating natural with harmlessness. Anyone who utilizes herbal products needs to understand a few basic safety rules. The fact that something is natural does not necessarily make it safe or effective. Although herbal remedies are generally perceived as harmless, reports of hepatotoxicity associated with herbal use are accumulating, suggesting they are not completely innocuous. On the basis of various case reports, the liver injury from herbal remedies has ranged from mild elevations of liver enzymes to fulminant liver failure requiring liver transplantation.

Herbal Remedies and Abnormal Liver Function Tests

Germander and Liver Damage: *Teucrium chamaedrys* (Germander) has been used as a remedy for weight loss and as a general tonic. Germander is an aromatic plant in the "mint family" and Germander tea made from the aerial parts of the plant had been in use for many centuries. Several cases of liver toxicity have been reported in Europe due to ingestion of germander has been associated with hepatotoxicity in humans including at least one fatality, and is restricted in the USA and several other countries. *Teucrium* is not in general use or available in commerce, although adulteration of other species with *Teucrium* due to mistaken identification has been reported. Evidence suggests that the relevant diterpenoids are metabolized via CYP3A4. (De Smet PAGM, et al. 1997, 137.)

Case of Germander toxicity: Bosisio, et al. reported a case of 55-year-old woman taking 1600 mg per day of germander became jaundiced after six months. Her bilirubin was 13.9 mg/dL, AST 1180 U/L, ALT 1500 U/L, ALP 164 U/L. Serological tests for all hepatitis was negative. Liver biopsy suggested drug induced hepatitis. Germander therapy was discontinued and hepatitis resolved in two months. Bosisio et al also described a HPLC method for detection of teucrin A, the active component of germander in beverages.

Chaparral and Liver Damage: *Larrea tridentata* (Chaparral) used as an anti-oxidant and anti-

cancer herbal product. Leaves, stems and bark in bulk are also available for brewing tea, however it was subject of FDA warning following several reports of hepatotoxicity. Controversy surrounded the reports of Chaparral toxicity and four cases reviewed by Watts C, et al. in 1994 were also associated with pre-existing liver conditions. (McGuffin M, et al.(eds.) 1997, 67.)

Some cases of chaparral toxicity: 1. A 45-year old woman took Chaparral 160 mg/day for 10 weeks presented with jaundice, anorexia, fatigue, nausea and vomiting. Liver enzymes and other liver function tests showed abnormally high values (ALT 1611 U/L, AST 957 U/L, Alkaline Phosphatase 265 U/L, GGT 993 U/L and bilirubin 11.6 mg/dL). Viral hepatitis, CMV and EBV were ruled out. Liver biopsy showed acute inflammation with neutrophil and lymphoplasmacytic infiltration, hepatic disarray and necrosis. The diagnosis was drug induced cholestatic hepatitis which in this case was due to use of Chaparral.

2. Gordon, et al. reported a case where a 60 year old woman took Chaparral for 10 months and developed severe hepatitis for which no other cause was found. On admission her bilirubin was 12.4 mg/dl, ALT 341 U/L, AST 1191 U/L and alkaline phosphatase 186 U/L. All tests for viral hepatitis were negative. Eventually she received a liver transplant.

Acorus spp. and Asarum spp. and Liver Damage: *Acorus* spp. and *Asarum* spp. both contain beta-asarone, a volatile ally benzene which can form a hepatotoxic and genotoxic epoxide metabolite when activated by hepatic microsomal enzymes. Adverse reactions of nausea and vomiting have been reported. These herbs are used primarily by professional herbalists: they are considered safe providing therapeutic dose ranges are observed. (McGuffin M, et al. (eds.) 1997, 134.)

Kava-Kava and Liver Damage: Kava, or *Piper methysticum*, is a plant root frequently used to lessen anxiety. It is well-known in South Pacific cultures as a ceremonial drink. Kava has become a controversial botanical remedy due to reports of potentially serious side effects, including liver damage.

Mechanism involved in hepatotoxicity induction: Heavy consumption of kava has been associated with increased concentrations of glutamyltransferase (GGT) suggesting potential hepatotoxicity. Also, several kava lactones may act as inhibitors of CYP 450 system (CYP1A2, 2C (, 2C19, 2D6, 3A4 and 4A9/11). Therefore, potential drug interactions with kava are likely.

Interactions: Interactions between kava and CNS depressant, alcohol, levodopa, caffeine, anticonvulsants and MAO inhibitors have been reported. In addition to hepatitis and liver failure due to chronic use of kava, a recent publication reports a case of acute kava overdose resulting in altered mental status and ataxia similar to that seen with ethanol intoxication.

Some cases of kava toxicity:

Escher, et al. described a case in which severe hepatitis was associated with kava use. A 50-year-old man took three to four kava capsules daily for two months (maximum recommended dose three capsules). Liver

function tests showed 60-70 fold increases in AST and ALT. Tests for viral hepatitis (HAV, HBV and HCV) were all negative as were tests for CMV and HIV. The patient eventually received a liver transplant.

Humberston, et al. also reported a case of acute hepatitis induced by kava-kava. Other cases of hepatotoxicity due to the use of kava have been documented.

In January 2003, kava extracts were banned in the entire European Union and Canada and also in the USA, the FDA strongly cautioned against using kava. There are at least 11 cases of serious hepatic failure and four deaths directly linked to kava extract consumption and there are also 23 reports indirectly linking kava with hepatotoxicity. Anke and Ramzan recently reviewed hepatotoxicity due to use of kava.

Previously, results of scientific studies on kava and the liver were contradictory or inconclusive. Theories exist concerning problems with kava extraction methods, kava root contamination and plant varieties. As a result, its sale and use are banned in many countries, but kava is not yet banned in the United States.

Mistletoe and Liver Damage: Mistletoe is a parasitic evergreen plant that lives on trees such as oaks, elms, firs, pines, apple and elms. Mistletoe was used in the folk medicine as a digestive aid, heart tonic and a sedative. It was also used in treating arthritis, hysteria and other mental disturbances. It was also used in the treatment of cancer. Usually, leaf of mistletoe is used in herbal remedy.

A case of Mistletoe toxicity: A 49-year-old woman presented with nausea, general malaise and a dull pain in the abdomen. Liver tests suggested hepatitis: Alt, 123 U/L, LDH 395 U/L, AST 250 U/L. Liver biopsy also suggested hepatitis. However, all tests for viral hepatitis were negative. The patient was diagnosed with a drug-induced hepatitis due to the use of mistletoe LipoKinetix and Liver Damage: LipoKinetix has been promoted for weight loss by increasing metabolism and as an alternative to exercise. Mechanism of action:

This product contains phenylpropanolamine (which is banned by the FDA in all over-the-counter cold medications), caffeine, yohimbine, diiodothyronine and sodium usniate. Usnic acid is derived from lichen and has antibacterial properties. It is used in skin cream and mouthwash. Sodium usniate found in LipoKinetics is derived from usnic acid. Liver toxicity due to use of usnic acid has been documented in medical literature

A case of LipoKinetix toxicity:

In 2002, seven patients who were using LipoKinetix developed acute hepatitis. Liver toxicity due to use of usnic acid has been documented in medical literature.

Moreover, usnic acid is present in Kombucha Tea (also known as Manchurian Mushroom or Manchurian Fungus tea), which is prepared by brewing Kombucha mushrooms in sweet black tea. Acute liver damage due to drinking this tea has been reported. There may be inherent susceptibility to usnic acid toxicity due to genetic predisposition. In addition, LipoKinetix also contains an ephedra alkaloid phenylpropanolamine which may also contribute to hepatotoxicity of this herbal supplement.

The FDA has warned consumers not to take LipoKinetix). Herbalife®, also promoted for weight reduction, may also cause liver injury.

Pennyroyal and Liver Damage: Pennyroyal, a mint oil with strong fragrance is used in aromatherapy or as a bath additive. Pennyroyal is used in folk medicine for inducing abortions, but pennyroyal oil contains several components including pulegone, a liver toxin.

Mechanism involved in hepatotoxicity induction: Pulegone is metabolized by the liver to a more toxic compound methofuran and is known to deplete glutathione in the liver. The toxicity is similar to that induced by overdose of acetaminophen (found in Tylenol® and many other medications). Therefore, pennyroyal oil should never be ingested. Pennyroyal tea which is prepared from the same herb is also toxic and causes both hepatic and neurologic damage.

Some cases of Pennyroyal toxicity:

An infant died after 7 receiving pennyroyal tea, and another infant developed severe liver disease. Also, there are reports of severe toxicity from pennyroyal oil in adults.

One woman who used pennyroyal oil for inducing an abortion developed multi-organ failure and then died.

Interestingly, N-acetylcysteine which is used to treat acetaminophen toxicity is also useful in treating toxicity due to ingestion of pennyroyal oil. In other published papers, the authors reviewed 18 different cases of pennyroyal toxicity and concluded that even ingestion of as little as 10 milliliter of pennyroyal oil may cause severe toxicity. In addition, one of two patients the authors studied in detail also died from ingestion of pennyroyal oil. There are occasional reports of skin problems (contact dermatitis) following use of pennyroyal oil.

Black Cohosh and Liver Damage: Black cohosh is primarily indicated for alleviating symptoms of menopause and sometimes for weight loss. There are several reports of liver toxicity from using black cohosh including two persons requiring liver transplant. In most cases, high serum bilirubin and liver enzymes are observed in patients after they start taking black cohosh.

A case of Black Cohosh toxicity: In one report a 50 year-old woman started taking black cohosh to get relief from postmenopausal symptoms. She later developed fatigue and abdominal pain, and her liver disease was due to the use of black cohosh. After she stopped taking black cohosh, she recovered.

Recently, regulatory agencies in Australia, Canada and the European Union have release statement regarding potential association between use of black cohosh and liver toxicity. The Dietary Supplement Information Expert Committee of the United States Pharmacopeia determined that products containing black cohosh should have warning label on the product.

How Herbal Medicines Affects liver? An herbal medicine can affect laboratory test results by one of the four mechanisms.

Physiological effects: Either through toxicity or enzyme induction due to an herbal product. For example, Kava-

Kava causes liver toxicity and elevated ALT, AST and bilirubin concentrations may be observed in healthy individuals taking Kava-Kava.

Direct assay interference most commonly with the immunoassays due to cross-reactivity of a component or components present in the preparation. For example falsely elevated digoxin level may be observed using the fluorescence polarization immunoassay (FPIA) for digoxin due to ingestion of Chinese medicine Chan Su, Lu-Shen-wan or Danshen.

Drug-Herb Interactions: Like drug-drug interaction, drug-herb interaction can be either pharmacokinetic or pharmacodynamic in nature: Example, St. John's wort can reduce efficacy of many drugs by increasing clearance through activation of cytochrome P-450 mixed function oxidase system.

Effects of contaminants in herbal products: An herbal product may contain undisclosed drugs and an unexpected drug level (such as phenytoin in a patient that never took phenytoin but took a Chinese herb) may confuse the laboratory staff and the clinician.

CONCLUSION

Drug-induced hepatotoxicity will remain a problem that carries both clinical and regulatory significance as long as new drugs continue to enter the market. Unfortunately, recognizing toxicity of specific drugs is limited by the relatively rare overall incidence of hepatotoxicity as well as underreporting. Models of toxicity and genomic predictors hold potential promise in preventing toxicity before it occurs. Administration of drugs in patients with underlying liver disease involves a balanced assessment of risk benefit ratio that may in fact favour judicious use when clear indications are present, as in the case of statins. Careful monitoring for drug interactions is especially important in patients who have undergone liver transplantation.

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