

Review Article

Conventional Drugs and Herbal Medicines Showing Hepatotoxicity: A Review

Sameer Rastogi*, Vijay Bhalla and Vandana Arora

School of Pharmacy, Lloyd Institute of Management & Technology, Plot no# 11,
Knowledge park 2, Greater Noida, Uttar Pradesh-201306, India.

ABSTRACT

In the medical field with the abilities of various synthetic drugs and medicinal plants-that are formulated in various elegant pharmaceutical forms-that are circulating in both our own countries and abroad. It initially gives an idea about the prevalence of drugs-induced hepatotoxicity in some countries and then it describes the various physiological functions of the liver. It also discusses the various mechanisms through which chemicals induce toxic and allergic hepatotoxicity and other disturbances such as cholestasis, granulomatous hepatitis, phospholipidosis, steatohepatitis, fibrosis, cirrhosis and tumors. For each of these diseases numerous examples of synthetic drugs and medicinal plants are given. With regard to medicinal plants, the Latin and Trade names, botanical families, uses and active constituents responsible for the induction of the hepatotoxicity are also given. The possible methods available for diagnosis and treatment of such diseases are given. The review then draws the attention to the fact that withdrawal of these drugs and medicinal plants from the pharmaceutical register does not limit the effective treatments of the various diseases for which these chemicals are indicated.

Keywords: Hepatotoxicity, Hepatic cholestasis, Herbal medicine, Conventional drugs.

INTRODUCTION

The liver performs numerous functions including bile formation and secretion, synthesis of a range of proteins including clotting factors, detoxification of drugs, xenobiotics and endogenous compounds, storage of vitamins, minerals and regulation of blood glucose. It consists of four main types of cells. The hepatocytes are the biosynthetic engines of the liver. Their important Golgi system and rough endoplasmic reticulum allow them to synthesize and secrete an array of proteins and metabolic enzymes. The endothelial cells line the sinusoids and serve as a barrier between the blood and hepatocytes. Two additional cell types line the sinusoids: They include Kupffer's cells, which are capable of removing and phagocytizing old and defective blood cells, bacteria and other foreign materials, and Stellati cells, which store fat and vitamin A¹.

Reports in the literature showed that incidences of hepatotoxicity associated with drug use accounted for 10.7% in USA², 2.85% in United Kingdom³, 4.2% New Zealand⁴ and 9.7% in France⁵. Nowadays complementary alternative medicine is increasingly used in various parts of the world. It includes dietary, nutritional and life styles changes together with

a separately mind and body control measures, cauterization, manual healing and biological treatments with animal, sea and herbal products. The latter are produced in various pharmaceutical forms including pills, capsules, tablets, powders, syrups and suppositories. Of all the alternative medicines, herbal products are gaining wide spread popularity for two reasons. Firstly, their production and presentation to the public in elegant pharmaceutical forms that resemble the synthetic and well-studied pharmaceutical products and secondly to the purported mistaken belief that herbal medicines are natural and bear no harm or toxicity to the human body. However, it should always be remembered that some herbal therapies are really toxic and can induce hepatotoxicity or even death. It should be noted that, for instance, in Asiatic countries, where some statistics are reported, herbal medicines-induced hepatotoxicity reached 30% of all reported drug-induced liver diseases⁶. This review will present some evidence regarding this aspect.

Biotransformation of drugs in the liver

The liver's unique metabolism makes it an important target of the toxicity of drugs and

xenobiotics. Most of these compounds enter the body through the gastrointestinal tract with minority absorbed directly through the lung or skin or by parenteral route. The greater part of drugs and xenobiotics are lipophilic, and can easily cross the membrane of intestinal and the hepatocyte cells. Drugs are rendered more hydrophilic by enzymatic action in the hepatocyte, yielding water-soluble products that are excreted in the urine or bile⁷. The pathways of drug metabolism can be classified as either phase I reactions (i.e. oxidation, reduction and hydrolysis) mediated by various cytochrome P450 isozymes, and/or phase II conjugation (i.e. glucuronidation, acetylation, sulphation and methylation), mediated by a variety of transferases. For highly polar drugs such metabolism is unnecessary. Some drugs may break down spontaneously. In most instances, metabolites generated by means of these reactions are either pharmacologically inactive or highly reactive. Based on their chemical character these metabolites may bind covalently to cellular macromolecules resulting in the formation of toxic oxygen species or react with membrane lipids to form lipid peroxides⁸.

Other metabolic pathways for biotransformation of many compounds involve glutathione and possibly other antioxidants (e.g. vitamin E and ascorbic acid). Glutathione is a thiol-containing tripeptide capable of binding to potentially harmful electrophilic compounds through glutathione-S-transferase, and thus plays an important role in protecting the cell from these toxic species⁹. Likewise, altered pharmacokinetics variables resulting from genetic influences, sex, age, and other conditions such as diabetic, hepatic and renal diseases may influence the metabolic outcomes, and predispose patients to toxic reactions to many drugs¹⁰⁻¹². Multiple factors are also often implicated, the most frequently being enzyme induction. Common inducing agents of certain P450 enzymes include phenobarbital, phenytoin, rifampicin as well as cigarette smoking.

Pathogenesis of hepatotoxicity

Drug or herbal medicines-induced hepatic damage is divided into several types that include:

a. Toxic hepatic damage

This type of damage is initiated via the interaction of the drug or the active component(s) of the herb with hepatic cytochrome P450 enzymes to produce electrophilic molecules or oxygen radicals that interact with the hepatic cells membranes

and/or enzymes leading to the damage and necrosis of the hepatocytes¹³. In addition, the drug may act to elevate the intracellular Ca²⁺ concentration resulting in damage of the hepatic mitochondria and the membranes integrity¹⁴.

The classical example of such hepatic damage is that produced by high doses of paracetamol (acetaminophen)¹⁵. The normal metabolism of the therapeutic doses of paracetamol involves sulphate conjugation via glutathione and excretion in the urine¹⁶. However, following acute or chronic consumption of high doses of paracetamol, the normal conjugation pathway is exhausted due to the depletion of glutathione and another cytochrome P450-pathway operates to produce a toxic highly reactive metabolite *N*-acetyl-*p*-benzoquinoneimine (NABQI). The latter interacts covalently with protein molecules in the hepatocytes leading to cell degeneration and death¹⁷. Paracetamol-induced hepatotoxicity is characterized by very high elevation of blood alanine and aspartate aminotransferases levels- over 3500 I.U per liter¹⁸. Other symptoms include severe hepatocytes damage, metabolic acidosis, renal insufficiency and damage, coma, thrombocytopenia and pancreatitis. Such type of hepatotoxicity is aggravated by concomitant use of phenytoin, isoniazid, starvation or chronic alcohol consumption^{19, 20}. The standard antidote for such hepatotoxicity is *N*-acetylcysteine which is highly effective in replenishing the depleted glutathione stores and preventing further hepatic injury even when administered 10 hours following paracetamol ingestion²¹. Similar glutathione depletion-induced hepatotoxicity is observed following excessive consumption of mescaline and cocaine²². Other drugs that are shown to induce toxic hepatic damage included the selective serotonin reuptake inhibitor and antidepressant citalopram^{23, 24}, the macrolide erythromycin analogue roxithromycin^{25, 26} and the anthraquinone laxatives²⁷.

With regard to the herbal medicines, many plants have been shown to induce toxic hepatic damage. Table 1 depicts some of the most famous plants that are available as herbal medicines in various pharmaceutical forms. The Table also shows the generic and Latin names of the plant, its active constituents and its purported uses.

b. Allergic hepatic damage

Allergic hepatic damage is usually caused by the antigen formed via the combination of a hapten of the drug or the active constituent of a herb with a specific liver protein³⁶. The

efficacy of such combination to culminate in an active antigen depends upon the human leukocyte antigen (HLA) configuration which is genetically determined^{42, 43}. The newly formed antigen is then processed by the human macrophages and presented to the CD⁴ cells that initiate the immune response that involves both humoral and cellular immunities. The produced antibodies then bind to the membranes of the hepatocytes. The antigen antibody reaction then results in hepatic damage that is accompanied by skin rash, urticaria, fever, gastrointestinal upset, jaundice and hepatomegaly.

Several drugs are shown to induce allergic hepatic damage. These include the combination of amoxicillin-clavulanate, sulphonamides, diphenylhydantoin⁴⁴ and the anti HIV-I drug nevirapine^{45, 46}.

With regard to herbal medicines some plants have been shown to induce their hepatotoxicity via this allergic reaction. These include *lilicium lanceolatum* (or Mang Cao), *Lycopodium serratum* (or Jin Bu Huan), *Tripterygium wilfordii* and the Germander herb *Teucrium chamaedrys*. (For constituents and use see also Table-1).

c. Idiosyncratic Hepatotoxicity

Some of the well established drugs have been reported to induce non-allergic hepatotoxicity that is unpredictable. It is believed to result from metabolic aberrations. The reaction latent period takes from weeks up to months following use of the drug. It can be differentiated from allergic hepatotoxicity by the absence of fever, rash or eosinophilia. Some of the drugs that have been shown to induce such hepatotoxicity are: isoniazid, valproic acid, ketoconazole, methyldopa and diclofenac^{47, 48}. No reports concerning medicinal herbs are revealed.

d. Hepatic cholestasis

As mentioned above, one of the liver functions is synthesis of bile salts and their passage into the gall bladder to be secreted into the duodenum. These comprise the salts of the primary bile acids such as cholic and chenodeoxy cholic acids which are conjugated with glycine or taurine and from which the secondary bile acids such as deoxycholic acid, lithocholic acid and urosodeoxycholic acid are formed by the action of the resident bacteria⁴⁹. Some drugs have the ability to interrupt bile flow and secretion from the hepatocytes into the gall bladder via binding of the bile salts in the liver or by interaction with the bile salts transporting proteins. This results in the accumulation of the bile inside the liver with

the concomitant cholestasis and appearance of high level of bilirubin in the blood and precipitation of jaundice. The hepatocytes are usually undamaged. However, if such cholestasis is accompanied by failure of canalicular and other intracellular processes, the toxic bile acids will accumulate within the hepatocytes leading to their damage. The damage may also extend to the bile ducts⁵⁰. Thus, mixed hepatotoxicity can ensue. In normal hepatic cholestasis, the patient suffers from jaundice together with fever, skin rash and arthralgia with an elevation of ALT enzyme and prolongation of prothrombin time. In the mixed hepatotoxicity one can observe capillary cholangiectasis, reduction in microvilli, formation of microbiliary thrombosis, liver cells degeneration, and necrosis and bile sedimentation. Many synthetic widely used drugs are known for their ability to induce hepatic cholestasis of the non-mixed type. These include chlorpromazine, hydrochlorothiazide, tenoxicam, estrogens, erythromycin, ibuprofen, captopril, prochlorperazine, clarithro-mycin, ticlopidine, terfenadine, amoxicillin-clavulanate, cotrimoxazole, tetrahydrocannabinol and parenteral nutrition⁵¹⁻⁵⁴ metformin⁵⁵, cyproterone⁵⁶, pravastatin^{57, 58}. However, both lovastatin⁵⁹ and atorvastatin^{60, 61} induce toxic acute hepatitis. Drug-induced mixed hepatic damage is observed following use of metformin, carbamazepine, cyclosporine, amoxicillin-clavulanate, fenofibrate and methimazole.

With regard to medicinal herbs several plants have been implicated in the induction of cholestatic hepatitis. These are shown in Table 2. Others have been shown to induce mixed hepatic damage necrosis and cholestasis. Some of these are shown in Table 3. In contrast some plants can suppress or treat cholestatic hepatitis. An example of these is *Balanitis aegyptica* bark extract⁶².

e. Granulomatous Hepatitis

Granulomatous hepatitis is characterized by infiltration of inflammatory cells and granulomatous changes in the hepatic parenchyma and the portal region. There are small rounded foci of epithelioid cells and round cells with multi-nucleated giant cells which may be surrounded by eosinophils. It may be accompanied by low grade fever and chronic fatigue. These symptoms are also present in cases of sarcoidosis and tuberculosis⁷³. It is now known that chronic use of various drugs induces this type of hepatotoxicity. These include: ticlopidine⁷⁴, allopurinol⁷⁵, carbamazepine^{76, 77}, aspirin⁷⁸,

paracetamol⁷⁹, dicloxacillin⁸⁰, glibenclamide⁸¹, rosiglitazone⁸², norfloxacin⁸³, nitrofurantoin⁸⁴, procainamide⁸⁵, mebendazole⁸⁶, methimazole⁸⁷, phenytoin⁸⁸, hydralazine⁸⁹, diltiazem⁹⁰, methyl dopa⁹¹, sulfonamides⁹², and amoxicillin-clavulanic acid⁹³.

With regard to the natural products it has been reported that intake of quinine⁹⁴ and quinidine⁹⁵ or consumption of ground and squeezed young leaves of barley used as a supplementary nutrient under the generic name "Green juice" induced granulomatous hepatitis with excessive elevation in both AST and ALT enzymes⁹⁶.

f. Hepatic Veno-occlusive disease

Hepatic Veno-occlusive disease results from closure or obliteration of the small intrahepatic veins by loose connective tissues in absence of thrombi. It is a progressive disease that leads to massive hepatocellular necrosis. It is usually observed as hepatomegaly, ascites and jaundice and weight gain⁹⁷.

With regard to drugs it is usually induced by high doses of some anticancer drugs such as azathioprine, cyclophosphamide, thioguanine and combination of cis-platinum-cyclophosphamide and dicarbazine⁹⁸.

Concerning the medicinal herbs, two of them have been reported to induce hepatic venoocclusive disease. The first is the herbal medicine which is known as "Black Cohosh" which composed of an infusion of the herbs *Heliotropium*, *Senecio* and *Crotalaria species*. The major constituents of these herbs are pyrrolizidine alkaloids⁹⁹. The second one is the medicinal tea which is known in trade as the Jamaican "Bush Tea". It is composed of an infusion of the medicinal herb Comfrey that is claimed to be an effective treatment for gastrointestinal pain¹⁰⁰. It is known by the Latin name *Symphytum officinale* and contains various pyrrolizidine alkaloids such as symphytine, intermedine, echimidine and symglandin.

g. Hepatic phospholipidosis

Phospholipidosis is a minor hepatic disease that is induced by some amphophilic drugs that have a tendency to accumulate within the lysosomes and interact with their phospholipids resulting in suppression of lysosomal function. It also induces hepatomegaly¹⁰¹. Amiodarone is one of the drugs known to induce such disturbance¹⁰². There are no reports about medicinal plants causing this hepatic disturbance.

h. Non- Alcoholic Steatohepatitis

Non- alcoholic steatohepatitis is usually described as fatty liver with inflammation and necrosis in absence of alcohol consumption. It is believed to be due to excessive release of free fatty acids released from the accumulated hepatic triglycerides. It is accompanied by a decrease in S-adenosyl methionine that protects the liver against fatty degeneration^{103, 104}. It is accompanied by an elevation in hepatic aminotransferases and hepatomegaly and may predispose to liver fibrosis and cirrhosis^{105, 106}. It is usually observed in patients with obesity, diabetes mellitus type 2 or hyperlipidemias and mostly in patients with insulin resistance. Various drugs have been shown to induce this disease. These include: amineptine and valproate¹⁰⁷; olanzapine and risperidone¹⁰⁸; tamoxifen¹⁰⁹, corticosteroids [prednisolone¹¹⁰ and methylprednisolone¹¹¹], amiodarone, zidovudine¹¹², didanosine (2, 3-dideoxyinosine)¹¹³ and high doses of tetracycline and aspirin and parenteral nutrition. There are no reports for herbal medicines, to induce this condition.

i. Liver Fibrosis and Cirrhosis

Some drugs have been shown to induce direct liver fibrosis and cirrhosis without inducing any elevation in hepatic aminotransferases or blood bilirubin. However, portal hypertension may be precipitated. These include high doses of methotrexate¹¹⁴, methyl dopa¹¹⁵, and vitamin A¹¹⁶. With regard to plants, however, various plants that belong to the genus *Senecio*, family Asteraceae e.g. *Senecio aureus*, *S. bicolor* and *S. vulgaris* have been observed to induce liver cirrhosis¹¹⁷.

j. Liver Tumors

Sporadic reports point to the involvement of some drugs in inducing hepatic carcinogenicity but there is controversy in this aspect. The accused drugs are methotrexate¹¹⁸, cyclosporine¹¹⁹ and nitrofurantoin¹²⁰. However, in herbal medicines most of the plants that contain pyrrolizidine alkaloids e.g. heliotrine and indicine have been positively linked with induction of hepatic cancer. These include those herbs that belong to the genus *Heliotropium*, family Boraginaceae such as *Heliotropium arborescens*, *H. popvii*, *H. lasiocarpium*, *H. eichwaldii*, *H. indicum* and *H. bacciferum*¹²¹ and those plants that belong to the genus *Senecio*, family Asteraceae which are medicinally used for inducing diuresis and diaphoresis. Such as *Senecio aureus*, *S. bicolor*, *S. jacobaco*, *S. vulgaris*, *S. douglasii* and *S. dofonicum*. This *Senecio* genus of herbs contains various pyrrolizidine alkaloids

such as senecionine, riddeline, retrorsine, floridanine, monocrotaline and otosenine. Other medicinal plants that also induce liver cancer include *Aristolochia bracteata* that belongs to the botanical family Aristolochiaceae and contains aristolochic acid and magnoflorine. Others are *Lingularia dentata*, *L. intermedia*, *Crotalaria albida* and *C. tetragona* which belong to the botanical family Asteraceae.

Diagnosis of the hepatotoxicity

The initial steps in diagnosis of the drugs and medicinal herbs-induced hepatic damages are:

- 1) Thorough grasping of the patient's medical history that include the types of drugs and/or herbal medicines used together with their doses frequency and duration of their use.
- 2) The medical health of the patient should be considered.
- 3) Various biochemical parameters should be measured. These include measurement of blood levels of bilirubin, hepatic transaminases e.g. aspartate aminotransferase (AST) and alanine aminotranferase (ALT) together with γ -glutamyl transpeptidase and alkaline phosphatase enzymes.
- 4) All diseases known to induce hepatotoxicity similar to drugs and medicinal herbs-induced hepatotoxicity such as sarcoidosis and tuberculo-sis should be excluded.
- 5) Performance of serological tests to check the presence and absence of the following anti-bodies:
 - i. IgM antihepatitis A virus
 - ii. Antihepatitis B/and C viruses
 - iii. IgM anticytomegalovirus
 - iv. IgM anti Epstein-Bar virus capsid antigen

- v. Herpes simplex virus
- vi. Anti-nuclear
- vii. Anti-mitochondrial

Besides these, the presence or absence of hepatitis B surface antigen and hepatitis C RNA should be examined.

- 1) Performance of ultra-sound guided percutaneous liver biopsy.
- 2) If possible the response to re-challenge with the suspected drug should be performed.

Treatment of Hepatotoxicity

Generally there is no established treatment for drugs- or herbs-induced hepatotoxicity. The best that can be done is the withdrawal of the offending drug or herb. Beside these, it can be pointed that some benefits have been observed with corticosteroids in allergic hepatotoxicity and with betaine, clofibrate and ursodeoxycholic acid¹²² and metformin¹²³ for non-alcoholic steatohe-patitis. Of all of drugs-induced hepatotoxicities, the only one that can be effectively treated is that of paracetamol via use of *N*-acetylcysteine .

CONCLUSION

This review clearly attempted to reveal the seriousness of the problems of drugs and herbal medicines-induced hepatotoxicity and pin pointed the limitations of its treatment. Thus, it remains for the health authorities in various countries to re-consider the registration of all those drugs and all approved medicinal herbs that have been shown in this review and others to induce or even predispose to hepatotoxicity. All of the medications mentioned in this review are not unique. Several of their better substitutes are already registered in various parts of the world. Thus care must be taken when these drugs are used for long times. This should be under the direction of physicians with careful monitoring of liver function.

Table 1: Medicinal Plants That Induce Toxic Liver Damage

Generic or Trade names	Latin name	Botanical family	Constituents	Purported uses	Reference
Milkwort; Da gin niu cao.	<i>Polygala chinensis</i>	Polygalaceae	Chinensin, chnensinapathol	Sedative.	(28,29)
Germander	<i>Teucrium chamaedrys</i>	Labiatae	Iridoid glycosides: furanoditerpenoids	Antiobesity	(30,31)
Kava tubers	<i>Piper methysticum</i>	Piperaceae	Kava pyrones, Kavaine alkaloids	Antianxiety Antipsychotic	(32,33)
Impila	<i>Callilepis laureola</i>	Asteraceae	Atracytoloside; Carboxyatracycloside	Anthelmintic Antitussive	(34)
Comfrey	<i>Symphytum officinale</i>	Boraginaceae	Pyrrrolizidine alkaloids: Symphytine	Antigastrointestinal ailments	(35)
Colts foot	<i>Tussilago farfara</i>	Asteraceae	Pyrrrolizidine alkaloids: Senkirkine;	Treatment of lung	(36)
Lycopodium herb, Jin Bu Huan	<i>Lycopodium serratum</i>	Lycopodiaceae	Tetrahydropalmatine	Analgesic	(37)
Tripterygium Roots, leaves and flowers	<i>Tripterygium wilfordii</i>	Celasteraceae	Wilforgine; Triptolide	Male contraceptive	(38)
Polygonum herb; Shou Wu Pian	<i>Polygonum multiflorum</i>	Polygonaceae	Anthraquinones	Treatment of prostate cancer, hair loss	(39-41)

Table 2: Medicinal plants that induce cholestatic hepatitis

Generic or Trade names	Latin name	Botanical family	Constituents	Purported uses	References
Chaparral leaves; Creosote bush	<i>Larrea tridentata</i> ; (<i>Larrea divaricata</i> Covillea tridentate)	Zygophyllaceae	Nordihydro- guaiaretic acid	Anti-psoriasis; Anti-amoebic; Diuretic; Antioxidant	(63-65)
Cascara	<i>Rhamnus purshiana</i>	Rhamnaceae	Free Anthraquinones, anthraquinone glycosides	Laxative	(66)
Rhubarb	<i>Rheum cultorum</i>	Polygonaceae	Anthraquinones	Laxative	(67)
Senna leaves	<i>Cassia senna</i>	Fabaceae	Anthraquinone glycosides (Sennosides A and B)	Laxative	(68)
Polygonum Shou Wu Pian	<i>Polygonum multiflorum</i>	Polygonaceae	Anthraquinones	Treatment of prostate cancer	(39-41)

Table 3: Medicinal Plants That Induce Mixed Hepatic Necrosis and Cholestatic Hepatitis

Generic or Trade names	Latin name	Botanical family	Constituents	Purported uses	References
Kava Ka tubers	<i>Piper methysticum</i>	Piperaceae	Alkaloids (Kavaine)	Antianxiety, Antipsychotic	(32,33)
Coutarea herb Copalchi, Copaltra	<i>Coutarea latiflora</i>	Rubiaceae	Alkaloids	Treatment of diabetes mellitus Type II	(69)
Ephedra, Ma-Huang	<i>Ephedra sinica</i>	Ephedraceae	Ephedrine & related alkaloids	Anorexigenic to decrease body weight	(70,71)
Polygonum Shou Wu Pian	<i>Polygonum multiflorum</i>	Polygonaceae	Anthraquinones	Treatment of prostate cancer	(39-41)
Aristolochia	<i>Aristolochia bracteata</i>	Aristolochiaceae	Aristolochic acid Magnoflorine	Abortifacient	(72)

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