

Hepatotoxicological Aspects of Drugs: An Overview

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Abstract

Liver is the organ in the body which helps in the biotransformation of various drugs by converting them into the various nontoxic metabolites. The various signs and symptoms in patients suffering from the hepatotoxicity are abdominal pain, nausea, vomiting, yellowing of the skin, eyes and mucus membrane. Medicinal drugs, herbal drugs, and industrial chemicals are known to cause hepatotoxicity. A number of hepatoprotective herbs are known such as *Aegle marmelos* and *Annona squamosa*. The present review provides an overview about various hepatotoxicity inducer agents and herbal hepatoprotectives.

Keywords: Hepatotoxicity, alanine transferase, alanine transaminase, hepatoprotective

1. Introduction

Liver is the organ in the body which helps in biotransformation of various drugs by converting them into various nontoxic metabolites [1]. Various drugs used in the treatment of numerous ailments can cause hepatotoxicity in overdoses, which ultimately results in the dysfunctioning of

liver. The various signs and symptoms in patients suffering from hepatotoxicity are abdominal pain, nausea, vomiting, yellowing of the skin, eyes and mucous membrane [2]. These medicinal drugs can cause liver toxicity either by inhibiting the various microsomal enzymes responsible for metabolism of drugs or by inhibiting the mitochondria function [3]. High levels of alanine transferase and alanine transaminase enzymes indicate that a patient is suffering from hepatotoxicity. Prevention of liver toxicity is possible by regular monitoring of the liver enzymes. In cases where chances of hepatotoxicity caused by a particular drug are more than drugs causing hepatotoxicity are discontinued [4].

2. Medicinal drugs induced hepatotoxicity

2.1 Paracetamol induced hepatotoxicity

Paracetamol is a drug used in the treatment of fever and pain. Ingestion of paracetamol greater than 150 mg/kg is known to cause hepatotoxicity. Actually, paracetamol is metabolized by liver microsomal enzymes to a toxic metabolite called N-acetyl-p-benzoquinone imine. This toxic metabolite undergoes conjugation reaction with sulfate and glycouronic acid and after undergoing conjugation it gets eliminated out from the body. But, if the patient has ingested a high dose of paracetamol, in such cases sulfonation reaction becomes saturated and the toxic metabolite accumulates in the body causing dysfunctioning of liver cells by binding reversibly with the various proteins [5]

2.2 Methotrexate induced hepatotoxicity

Methotrexate is an immunosuppressant drug which also has the potential to induce hepatotoxicity. Prolonged use of this drug at a maintenance dose of 7.5 to 25 mg given weekly can induce hepatotoxicity. This drug causes hepatotoxicity by inhibiting the synthesis of DNA and RNA in the liver, which ultimately results in damage to liver cells or producing cellular arrest [6].

2.3 Isoniazid-induced hepatotoxicity

Isoniazid is an antimalarial drug which when administered at a dose greater than 1000 mg can cause hepatotoxicity. Isoniazid gets metabolized to monoacetylhydrazine. This monoacetylhydrazine further gets metabolized by the various cytochrome enzymes present in the liver to isonicotinic acid. This isonicotinic acid is a potent hepatotoxic agent [7].

2.4 Niacin-induced hepatotoxicity

Niacin at a dose more than 500 mg can cause hepatotoxicity. Amidation pathway is responsible for

the metabolism of niacin in the body, which leads to the formation of nicotinamide and pyrimidine metabolites. These metabolites are severe hepatotoxic agents, which cause damage to the liver cells by increasing the level of the aminotransferase [8]. It can also cause damage to the liver by causing hepatitis [9].

2.5 Aspirin-induced hepatotoxicity

Aspirin is used in the treatment of fever, inflammation and pain. It can also cause liver toxicity when administered in overdose. Aspirin in high dose causes dysfunctioning of the mitochondria, which ultimately results in a special form of liver toxicity known as Raye Syndrome. Aspirin can also cause liver toxicity by causing micro vesicular steatosis, which is defined as deposition of fat droplets in the liver [10].

2.6 Rifampicin-induced hepatotoxicity

Rifampicin also induces liver toxicity at dosage greater than 100 mg/kg. This drug causes liver toxicity by increasing the levels of bilirubin, cholesterol, and phospholipids in the liver [11].

2.7 Carbamazepine induced hepatotoxicity

Carbamazepine is one of the drugs having hepatotoxic potential and causes liver toxicity at a dose greater than 1000 mg. Carbamazepine undergoes oxidative metabolism in our body which results in the formation of various epoxides. These epoxides cause cholestasis hepatitis and also lead to severe hepatotoxicity [12].

2.8 Valproate-induced hepatotoxicity

Valproate also causes damage to the liver cells when administered at a dose greater than 500 mg. The mechanism by which it causes hepatotoxicity is that valproate and its metabolites affect beta oxidation of various fatty acids in the liver which is ultimately responsible for severe hepatotoxic reactions [13].

2.9 Diclofenac drug induced hepatotoxicity

Diclofenac at a dose more than 500 mg causes severe hepatotoxic reactions in the body. Glucouronidation is the pathway by which metabolism of diclofenac occurs in the body. During this metabolism acylglucouronide and 5-hydroxylglucouronide are the two unstable metabolites produced in our body. These two metabolites covalently bind to various self-antigen proteins present in the body. These bindings lead to the formation of neoantigen which causes the destruction of hepatocytes [14].

2.10 Lovastatin-induced hepatotoxicity

Lovastatin is a hyperlipidemic drug which when administered at a dose more than 80 mg can cause hepatotoxicity. This drug can cause liver toxicity either by inhibiting bile flow in the liver or by directly damaging the liver cells [15].

2.11 Haloethane-induced hepatotoxicity

Haloethane is another drug which when administered to the patient at dosage more than 500 mg causes severe hepatotoxic reactions. Haloethane is metabolized in our body by acetylation reactions to form the various triuroacetylated compounds. Trifluoroacetylchloride is one of the metabolite of haloethane which causes fulminant type of hepatitis in liver by forming neo antigen. These neo antigens produce liver damage by provoking an immunoresponse against the hepatocytes [16].

2.12 Sevoflurane-induced hepatotoxicity

Sevoflurane at a dose greater than 500 mg causes hepatotoxicity. This drug gets metabolized by the various liver microsomal enzymes to form various trifluoroacetylated compounds. These metabolites form various immunogenic adducts by binding with the various intercytoplasmic proteins. These immunogenic adducts cause hepatotoxic reactions [17].

3. Herbal drugs-induced hepatotoxicity**3.1 Aloe vera-induced hepatotoxicity**

The 500 mg of *aloe vera* extract intake for more than four weeks can cause liver toxicity. The pyrrolizidine alkaloids present in *aloe vera* causes hepatotoxicity. This drug causes liver damage by interfering with cytochrome enzymes present in the liver, which is responsible for causing the inflammation.[18]

3.2 Green tea-induced hepatotoxicity

Intake of more than three cups in a day causes liver toxicity. Epigallocatechin-3- gallate (EGCG) catechin present in green tea causes liver damage. It basically causes the liver dysfunctioning by causing damage to the membrane of mitochondria and by production of reactive oxygen species [19].

3.3 Comfrey-induced hepatotoxicity

Various alkaloids present in comfrey such as symphetamine, lycosamine are hepatotoxic. Comfrey oral intake of more than 100 mg is hepatotoxic. Various alkaloids presents in comfrey are

metabolized by liver cytochrome enzymes to toxic pyrrole which causes liver toxicity by causing damage to the endothelial cells [20].

4. Industrial chemicals induced hepatotoxicity

4.1 Carbon tetrachloride-induced hepatotoxicity

Carbon tetrachloride is a severe hepatotoxic chemical. It gets metabolized in the body to produce free radical named trichloromethyl. This free radical causes liver toxicity by causing peroxidation of the membrane lipids which ultimately effects the membrane integrity [21].

4.2 Ethanol induced hepatotoxicity

Ethanol causes severe hepatotoxic reactions by elevations in the level of CYP2E1 enzyme. This elevated enzyme causes cell necrosis by generating reactive oxygen species which produces oxidative stress [22].

4.3 Chloroform induced hepatotoxicity

Chloroform gets metabolized in our body to form phosgene gas. This phosgene gas formed causes hepatotoxicity by effecting glutathione present in the body and by covalently binding to various macromolecules [23].

5. Hepatoprotective herbs

5.1 *Aegle marmelos*

In Sanskrit *Aegle marmelos* is also known as Bilva. Its hepatoprotective effect in alcohol induced liver injury has been estimated in rats with the use of essential biomarkers [24].

5.2 *Annona squamosa*

Annona squamosa extracts (300 and 350 mg/kg bw) were utilized in studying their hepatoprotective effect against hepatotoxicity induced by isoniazid and rifampicin in albino Wistar rats model. Histopathological study revealed centrilobular region inflammation with portal triaditis and hepatocytic necrosis, while minimal inflammation was observed in treatment group with modest portal triaditis and normal lobular structure. So *A. squamosa* extract could be used as a hepatoprotective agent for treating chemical-induced hepatic destruction [25].

5.3 *Ficus carica*

The hepatoprotective activity of methanolic extract of *Ficus carica* leaves in CCl₄ induced liver damage was evaluated. A 500 mg/kg oral dose showed a considerable shielding effect as it

lowered serum levels of serum alanine transaminase (ALT), serum aspartate transaminase (AST), malonidialdehyde equivalent, and total serum bilirubin [26].

5.4 *Flacourtia indica*

Hepatoprotective properties of *Flacourtia indica* (aerial parts) extract were evaluated against paracetamol-induced hepatic necrosis. It was found that all extracts reduced ALT, AST, and serum alkaline phosphatase (ALP) [27].

5.5 *Glycyrrhiza glabra*

Glycyrrhiza glabra, also termed as licorice has triterpene saponin called glycyrrhizin, which shows vital hepatoprotective action. This is categorized into sulfated polysaccharides and numerous studies by Japanese researchers have shown its antiviral and hepatoprotective potential [28].

5.6 *Cichorium intybus*

In Ayurveda *Cichorium intybus* also termed as Kasni is used for the treatment of liver disorders in the form of hepatoprotective polyherbal preparations. In adult albino rats, extract of *C. intybus* (alcoholic) showed effective protection against chlorpromazine-induced hepatic injury. Cichorin, a bitter glucoside, is an active component of this herb.[29]

5.7 *Solanum nigrum*

In Ayurveda, *Solanum nigrum* is termed as Kakamachi. Herbal vendors widely prescribe the aromatic water extracted from it for liver disorders. Hepatoprotective activity of powdered extract of the plant has been reported by traditional practitioners however, little clinical evidence is available [30].

5.8 *Tephrosia purpurea*

Tephrosia purpurea is termed as Sharpunkha in Ayurveda. Its alkaline formulation is utilized for treating spleen and liver diseases. It demonstrated shielding action against D-galactosamine and carbon tetrachloride poisoning in animal models. The seeds, roots, and leaves contain deguelin, quercetin, and tephrosin. However, the hepatoprotective bioactive of the drug is still to be proved [30].

6. Conclusion

Hepatotoxicity is the severe condition in the body which results in the liver dysfunctioning and can cause the permanent damage to the liver of patient. Various herbal remedies, various chemical

used in the industries, various synthetic drugs can causes injury to the liver by various biochemical mechanism such as by inducing the damage to the mitochondrial membrane, inhibiting the liver microsomal enzymes, inhibiting the fatty acids oxidation process taking place in the liver. Various drugs usage is banned due to severe hepatotoxic reactions induce out by them such as the example is the nimusulide. But still such drugs are sale out in the Indian market. People use these drugs for the treatment of the pain and fever as buying of these drugs do not require any medical prescription. To prevent the severe hepatotoxic reactions induced out by these drugs, a proper withdrawal of these hepatotoxic drugs should be done from the market. Prescriber should carry out the proper monitoring of the liver enzymes in patients who are at the therapy of susceptible hepatotoxic drugs. Patients should be educated about the various signs and symptoms of the various hepatotoxic drugs which can happen to them during the administration of such drugs so that they can report to the prescriber immediately. Discontinuation of the drugs should be done in such cases to prevent out the severe liver injury.

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