A REVIEW ON DRUG INDUCED HEPATOTOXICITY AND ITS MANAGEMENT BY HERBAL DRUGS

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ABSTRACT
The liver plays vital functions in maintaining, performing and regulating the homeostasis of body and it involves in almost all biochemical pathways such as nutrient supply, reproduction, biotransformation, energy supply and growth. The liver metabolize, detoxify and activate exogenous as well as endogenous compound and is capable for transforming foreign chemicals as it has high level of enzymatic system. Liver disorder or injury is defined as conditions, diseases, or infections that influence the structure and/or function of liver and this can lead to pathophysiological changes which may results in many liver dysfunction such as hepatitis, cirrhosis etc. In US, drug induced hepatotoxicity is the main reason behind withdrawal and non-approval of drugs by FDA. The drug induced hepatotoxicity may divided into acute reactions (hepatocellular necrosis); cholestasis (with or without inflammation); and miscellaneous reactions. Documentation and analysis of various case reports and case series suggested many drugs are hepatotoxic such as isoniazid, rifampicin, halothane, chlorpromazine, amoxicillin-clavulanic acid etc. In early researches on DILI, Chlorpromazine & Halothane were commonly reported cause of drug induced liver injury.

KEYWORDS: Hepatotoxicity; Liver Injury; Hepatotoxic Drugs; Herbal Drugs.

INTRODUCTION
The liver plays vital functions in maintaining, performing and regulating the homeostasis of body and it involves in almost all biochemical pathways such as nutrient supply, reproduction, biotransformation, energy supply and growth. The main functions of liver are to metabolize fat, protein and carbohydrates; storage of vitamins, bile secretion and
The liver metabolize, detoxify and activate exogenous as well as endogenous compound and is capable for transforming foreign chemicals as it has high level of enzymatic system. Exogenous compounds such as drugs and endogenous compounds such as steroids are being metabolized by the liver in presence of various enzymes. The synthesis of bile, cholesterol, fibrinogens and albumin is performed by well-developed organelles system of liver. Liver disorder or injury is defined as conditions, diseases, or infections that influence the structure and/or function of liver and this can lead to pathophysiological changes which may results in many liver dysfunction such as hepatitis, cirrhosis etc. In US, drug induced hepatotoxicity is the main reason behind withdrawal and non-approval of drugs by FDA. It is estimated that more than 1000 drugs and chemicals are hepatotoxic and may lead to serious liver injury. Approximately, 50% of liver failure, 10% acute hepatitis and 5% hospitalization is due to drug induced liver injury. About 75% cases of idiosyncratic drug reaction causes liver transplantation or death. The common cause of acute liver disease is drug induced hepatotoxicity and accounts for about 10% mortality. In renal transplant subject with chronic liver diseases inefficient drug metabolism is observed and thus, these types of patients are more prone to drug induced hepatotoxicity. Documentation and analysis of various case reports and case series suggested many drugs are hepatotoxic such as isoniazid, rifampicin, halothane, chlorpromazine, amoxicillin-clavulanic acid etc. In early researches on DILI, Chlorpromazine & Halothane were commonly reported cause of drug induced liver injury. However, the data on liver toxicity of drugs were reported only in few case reports which are being used for decades and thus, the evidence of various hepatotoxic drugs are lacking. The drug induced hepatotoxicity may divided into acute reactions (hepatocellular necrosis); cholestasis (with or without inflammation); and miscellaneous reactions. However, some drugs may cause serious damage and can lead to tumor growth. The hepatotoxic reactions caused by drugs may be summarized as acute reactions (which consist of hepatocellular necrosis), cholestasis (with or without inflammation) and miscellaneous reactions; however, some drugs can cause chronic damage and may even lead to tumor growth. In this article, we have discussed the drug-induced hepatotoxicity, factors that may add to its toxicity, mechanism and prevention.
Table 1: Common hepatotoxic reactions.\cite{25}

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Hepatotoxic reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Acute, direct hepatocellular toxicity, chronic toxicity</td>
</tr>
<tr>
<td>Isoniazid; Methyldopa; Allopurinol; Aspirin; Quinidine; Sulfonamides; Valproate</td>
<td>Miscellaneous acute reactions</td>
</tr>
<tr>
<td>Amiodarone; Methotrexate; Niacin; Rifampicin; Pyrogallol; Vitamin A</td>
<td>Chronic toxicity</td>
</tr>
<tr>
<td>Chlorpropamide; Erythromycin-estolate; Phenybutazone</td>
<td>Acute cholestasis, phenothiazine type</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Acute, idiosyncratic hepatocellular toxicity</td>
</tr>
<tr>
<td>Halothane-related anesthetics; Indomethacin; Phenytion; Propylthiouracil; Hydrocarbons</td>
<td>Acute, direct hepatocellular toxicity</td>
</tr>
<tr>
<td>Tratcycline; Methyltestosterone; Oral contraceptives</td>
<td>Acute cholestasis, steroid type</td>
</tr>
</tbody>
</table>

Table 2: Classification of drug induced liver injury and drugs which have been associated with each pattern\cite{26}

<table>
<thead>
<tr>
<th>Pattern of liver injury</th>
<th>Associated drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Hepatocellular (ALT &gt;3× ULN)</td>
<td>Acarbose; Acetaminophen; Allopurinol; Bupropion; Bromfenac; Diclofenac; Fluoxetine; Isoniazid; Ketoconazole; Lisinopril; Losartan; Nefazodone; Nevirapine; Paroxetine; Pyrazinamide; Rifaximin; Risperidone; Ritonavir; Sertraline; Statins; Tetracycline; Trazodone; Troleandomycin; Valproic acid</td>
</tr>
<tr>
<td>Cholestatic (AP &gt;2× ULN, ALT/AP &lt;2)</td>
<td>Amoxicillin/clavulanate; Anabolic steroids; Azathioprine; Chlorpromazine; Clopidogrel; Cytarabine; Erythromycin; Estrogen; Fosinopril; Irbesartan; Phenothiazines; Sulindac; Terbinafine; Tricyclics</td>
</tr>
<tr>
<td>Mixed (elevated AP and ALT)</td>
<td>Amitryptilline; Azathioprine; Captopril; Carbamazepine; Clindamycin; Cyproheptadine; Enalapril; Flutamide; Ibuprofen; Nitrofurantoin; Phenobarbital; Phenytion; Sulfonamides; Trazodone; Trimethoprim; sulfamethoxazole; Verapamil</td>
</tr>
<tr>
<td>Chronic Steatohepatitis Microvesicular steatosis</td>
<td>Amiodarone; Tamoxifen NRTIs; Valproic acid; Tetracycline</td>
</tr>
<tr>
<td>Granulomatous hepatitis</td>
<td>Diltiazem; Sulfa drugs; Quinidine</td>
</tr>
<tr>
<td>Sinusoidal obstruction Syndrome</td>
<td>Busulfan; Cyclophosphamide</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Hepatic adenoma</td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Nitrofurantoin; Minocycline</td>
</tr>
</tbody>
</table>
### Table 3: Registries of drug-induced liver injury.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>461</td>
<td>784</td>
<td>300</td>
<td>1676</td>
<td>313</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>53</td>
<td>58</td>
<td>48</td>
<td>55</td>
<td>39.3</td>
</tr>
<tr>
<td>Females (%)</td>
<td>49</td>
<td>58</td>
<td>48</td>
<td>56.3</td>
<td>42</td>
</tr>
<tr>
<td>% with jaundice</td>
<td>71</td>
<td>73</td>
<td></td>
<td></td>
<td>65.5</td>
</tr>
<tr>
<td>% hospitalized</td>
<td>53</td>
<td>54</td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>% dead/transplanted</td>
<td>7</td>
<td>9.2</td>
<td>9</td>
<td>3.75</td>
<td>17.3</td>
</tr>
</tbody>
</table>

#### Injury pattern:

<table>
<thead>
<tr>
<th></th>
<th>Hepatocellular</th>
<th>Mixed</th>
<th>Cholestasis</th>
<th>Antibiotics (32%); CNS agents (17%); Musculoskeletal agents (17%); GI drugs (10%); Anti-TB drugs (7.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>55.9</td>
<td>52.2</td>
<td>26.2</td>
<td>Antibiotics (45%); CNS agents (15%); Immuno-modulators (5%); Analgesics (5%)</td>
</tr>
<tr>
<td></td>
<td>19.3</td>
<td>21.4</td>
<td>21.6</td>
<td>Antibiotics (45%); CNS agents (15%); Immuno-modulators (5%); Analgesics (5%)</td>
</tr>
</tbody>
</table>

#### Implicated drugs

- Antibiotics (32%)
- CNS agents (17%)
- Musculoskeletal agents (17%)
- GI drugs (10%)
- Anti-TB drugs (7.2%)

#### Potential Hepatotoxic Agents

**Statins**

Statins are lipid lowering drugs which widely used worldwide. It competitively inhibits HMG-CoA, which results in inhibition of process of cholesterol biosynthesis in liver. The LDL (low-density lipoprotein) level in decreased and thus increases the atherosclerotic plaque stability. One study concludes that, administration of high doses of statins in animal model shows biochemical abnormalities in liver function and statin derivatives, lovastatin and simvastatin on high doses causes hepatocellular necrosis. In human, hepatocellular necrosis by statins is rarely seen. Elevation of aminotransferase in liver with statin is usually dose-related which occurs with first twelve of therapy. The incidence of mild aminotransferase elevation upto 2-3×ULN associated with statin ranges from 0-3%. Elevation of ALT (ALT >3 × ULN) can occur with use of statins but the rate is low.

**Other lipid-lowering agents**

Ezetimibe inhibits intestinal uptake of cholesterol and has been used alone or in conjunction with other lipid-lowering agents for management of hyperlipidaemia. Clinical trials of ezetimibe in conjunction with statins demonstrated a higher (1.3%) rate of aminotransferase...
elevation (>3×ULN) compared with statins alone (0.4%). Two non-fatal cases of hepatotoxicity with ezetimibe used in conjunction with simvastatin have been reported recently. Cholestatic hepatitis was observed in one patient and a steroid-responsive autoimmune hepatitis was observed in another.

**Thiazolidinediones**

These are a class of insulin-sensitizing drugs which are used in management of diabetes mellitus through activation of the gamma-isoform of the peroxisome proliferator-activated receptor (PPARc). TZDs lower serum glucose and insulin levels, improve peripheral glucose uptake, and decrease triglyceride levels. Troglitazone was the first approved TZD and it was withdrawn from the market in 2000 because of 94 recorded cases of liver failure. An idiosyncratic mechanism of toxicity was suggested based on the delayed (3–7 months) onset of ALT elevation and a lack of dose effect. Rosiglitazone and pioglitazone second-generation TZDs, were introduced into the market. In early clinical trials of rosiglitazone and pioglitazone, rates of AST elevation >3 times the ULN were no different compared with placebo. Since then, various case reports of hepatotoxicity with both pioglitazone and rosiglitazone have been reported. These studies shown one report of fulminant hepatic failure with pioglitazone one case of granulomatous hepatitis with rosiglitazone and one case of fatal liver failure with long-term rosiglitazone use. Generally in patient with history of troglitazone toxicity, rosiglitazone and pioglitazone is not advised.

**Other antidiabetic agents: metformin**

Metformin is an oral biguanide hypoglycaemic agent which is widely used in management of non-insulin-dependent diabetes mellitus. In three case reports of metformin rare cases of hepatotoxicity was reported. These reports showed idiosyncratic hepatotoxicity mechanism and both cholestatic and hepatocellular toxicity were reported. Lactic acidosis is a rare complication associated with the use of metformin. The overall rate of metformin induced hepatotoxicity was 3-5 cases per 1,00,000 patients per year. Hepatic impairment is cited as a risk factor for lactic acidosis; however, pre-existing cardiac disease and renal insufficiency are more commonly implicated risk factors. The use of metformin in patients with hepatic impairment should be avoided due to increased risk of lactic acidosis.

**Antiretrovirals**

The incidence of hepatotoxicity in patients using antiretroviral therapy (ART) is ranges from 3–18%. The incidence liver failure can lead to death or transplantation is uncommon and
ranges from 1.1 patients per 1000 patients per year to 1.1 patients per 100 patients per year.\cite{55,56} All three classes of ART, nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) have been associated with hepatotoxicity.\cite{57}

**Protease inhibitors**

All PIs are metabolized by the cytochrome P450 3A4 system and have been associated with hepatotoxicity. Among the PIs, high dose of ritonavir is associated with the highest incidence of hepatotoxicity with 3–9% incidence of severe hepatotoxicity.\cite{58-61} Lower doses of ritonavir (<200 mg twice daily) used in boosting regimens have largely replaced high-dose ritonavir and have not been associated with increased hepatotoxicity except when used with amprenavir.\cite{62,63} Tipranavir, a newer PI, has been associated with reports of severe hepatotoxicity.\cite{64} A black box warning was issued in June 2006 warning of an increased risk of hepatitis and hepatic decompensation in patients taking tipranavir and ritonavir, especially in patients with HBV or HCV co-infection.

Both indinavir and atazanavir have been associated with asymptomatic indirect hyperbilirubinaemia due to competitive inhibition of bilirubin uridine diphosphate (UDP)-glucoronosyl transferase.\cite{65,66} Homozygosity for the uridine diphosphate (UDP)-glucoronosyl transferase genetic allele associated with Gilbert’s syndrome increases the risk of hyperbilirubinaemia\textsuperscript{a}8 from indinavir and atazanavir.\cite{67} Another allele, uridine diphosphate (UDP)-glucoronosyl transferase1\textsuperscript{a}6, has been shown to be associated with hyperbilirubinaemia in Thai patients treated with indinavir.\cite{68} Co-infection with viral hepatitis has not been associated as a risk factor for hyperbilirubinaemia in indinavir users.\cite{69} Current guidelines recommend avoiding use of indinavir in combination with atazanavir.\cite{70}

**Nucleoside reverse transcriptase inhibitors**

NRTIs are associated with hepatic steatosis and lactic acidosis. The spectrum of hyperlactataemia associated with NRTIs ranges from asymptomatic mild lactate elevation to a rare but potentially fatal lactic acidosis syndrome (LAS). Asymptomatic hyperlactataemia without metabolic acidosis is common in HIV-infected patients (8–18%), is often transient, and is non-specific for current NRTI use.\cite{71} Liver histology demonstrates mixed microvesicular and macrovesicular steatosis with use of NRTIs.\cite{72,73} The incidence of LAS is rare about 1.3–3.9 cases per 1000 patient per years.\cite{74} The mechanism of NRTI-associated lactic acidosis is hypothesized, to involve mitochondrial toxicity. Some in-vitro studies
suggests that, mitochondrial polymerase gamma, the enzyme which is responsible for the replication of mitochondrial DNA, is variably inhibited by NRTIs according to the following order: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir.\(^{[75]}\) In theory, this might explain the higher rates of lactic acidosis observed with stavudine, zalcitabine and didanosine. Current recommendations advise against co-administration of didanosine and stavudine due to an increased risk of lactic acidosis. Among HCV/HIV co-infected patients, administration of ribavirin in conjunction with didanosine or stavudine has been associated with mitochondrial toxicity and lactic acidosis.\(^{[64, 76]}\) Lesser rates of hepatotoxicity have been observed with abacavir, lamivudine and tenofovir.

**Non-nucleoside reverse transcriptase inhibitors**

The NNRTI class of antiretroviral agents includes nevirapine, efavirenz and delavirdine. Among these class of drug, nevirapine warrants particular attention with regard to hepatotoxicity. Nevirapine toxicity may manifest as a rash-associated hypersensitivity reaction (with or without concurrent hepatotoxicity) within the first few weeks of starting therapy in 2.3% of patients.\(^{[77]}\) A second, late onset toxicity related to cumulative dose over time is more commonly observed than a hypersensitivity reaction.\(^{[77-79]}\) Rare cases of hepatic failure leading to liver transplantation and death have been reported with nevirapine.\(^{[80]}\) Risk factors for hepatotoxicity include co-infection with HBV or HCV and higher CD4 counts associated with use in postexposure prophylaxis regimens.\(^{[78, 79]}\) Current guidelines recommend avoiding nevirapine in women with CD4 counts >250 and in men with CD4 counts >400.\(^{[64]}\) Two studies suggested a significantly lower risk of hepatotoxicity with efavirenz-based regimens compared with nevirapine-based regimens.\(^{[79,80]}\) whereas, another study showed no difference.\(^{[81]}\) Efavirenz has been safely substituted in patients who developed hepatotoxicity with nevirapine, suggesting that hepatotoxicity due to nevirapine is not class-specific.\(^{[82]}\)

**Antibiotics**

Antibiotics are a commonly and leading cause of DILI. A recent single US centre experience reported antibiotics as the class of drugs most frequently implicated in non-fulminant drug-induced hepatitis.\(^{[83]}\) Amoxicillin, clavulanic acid, minocycline, nitrofurantoin, trimethoprim, sulfamethoxazole and trovafloxacin were the most frequently implicated antibiotics. Antibiotics were cited as the most frequent cause of DILI in a recent Spanish registry, French study, and United Kingdom study.\(^{[84-86]}\) All forms of liver injury ranging from cholestasis
(amoxicillin/clavulanic acid) to autoimmune hepatitis (minocycline) to ALF (telithromycin) have been reported.

**Amoxicillin-clavulanic acid**

Amoxicillin-clavulanic acid is the most frequently reported antibiotic associated with drug-induced hepatotoxicity.\(^{[84-86]}\) The overall rate of symptomatic hepatitis due to amoxicillin-clavulanic acid is estimated at <1 in 1,00,000 persons exposed.\(^{[87]}\) The typical pattern of hepatotoxicity is a cholestatic reaction that develops 1–4 weeks after cessation of therapy.\(^{[88-91]}\) However, delayed onset of symptoms can be seen up to 8 weeks following discontinuation of therapy\(^{[89, 91]}\) and prolonged cholestasis with ductopenia following cessation of therapy has also been reported.\(^{[92]}\) A recent large prospective case series involving 69 patients with amoxicillin-clavulanate hepatotoxicity suggested that the type of hepatic injury observed varies according to the time from onset of therapy, where hepatocellular injury predominates at 1 week, cholestatic injury at 2–3 weeks and mixed liver injury after 3 weeks. There was a 7% probability of an unfavourable outcome (death, liver transplant or persistent liver damage) and a 3% probability of a severe (death or liver transplantation) outcome in this series.\(^{[91]}\) Immunological idiosyncrasy associated with certain HLA haplotypes may play a role in the pathogenesis.\(^{[92]}\)

**Anti-TB agents**

Upwards of 20% of patients on isoniazid (INH) develop elevated liver enzymes that do not progress during the course of therapy and in some case may resolve spontaneously.\(^{[93-96]}\) This form of tolerance or adaptation is common to many drugs and implies possible upregulation of cytoprotective mechanisms.\(^{[97]}\) However, there is an increased risk for INH-induced hepatic injury in patients who are older, drink alcohol, or are pregnant / postpartum, or malnourished, as well as those on other TB medications, including rifampin and pyrazinamide (PZA).\(^{[96, 98]}\)

**Rifampicin**

Hepatitis has been reported to occur 0.46% of individuals undergoing anti-tubercular therapy and receiving anti-tubercular drugs. The rate of hepatotoxic reaction was much higher in Indian patients as compared to that reported from developed countries.\(^{[99-101]}\) It is readily absorbed from the gastrointestinal tract (90%) and most of it is bound to plasma proteins in circulation. The involvement of oxidative stress in rifampicin-induced hepatotoxicity has been demonstrated previously in experimental rats.\(^{[102]}\) Rifampicin is a potent inducer of
cytochrome P450 action and enhances the covalent binding of reactive metabolites of acetyl hydrazine to the macromolecules of hepatocytes leading to hepatic cell damage.\textsuperscript{103, 104} Desacetylrifampicin, another reactive metabolite of rifampicin, also contributes to some of its adverse effects. It has been reported to modulate the membrane permeability and cause membrane damage.\textsuperscript{105} Its prolonged exposure significantly decreases glucose-6-phosphatase activity, which could be a reason for the increased level of lipid peroxidation.\textsuperscript{106-108} Anti-tubercular drugs increase intracellular calcium concentration leading to the induction of phospholipase A2 which degrade membrane phospholipids.\textsuperscript{109, 110} Additionally, CYP2E1 activation and fatty acid accumulation in the liver either due to excessive supply of lipids to the liver or interference with lipid deposition, has been documented in the anti-tubercular drug-induced liver disorders.\textsuperscript{109-111} Anti-tubercular drugs also induce hypercholesterolemia that might be due to increased uptake of LDL from the blood, by the tissues.\textsuperscript{112, 113} Hepatitis has been reported to occur 0.46% of individuals undergoing anti-tubercular therapy and receiving anti-tubercular drugs. The rate of hepatotoxic reaction was much higher in Indian patients as compared to that reported from developed countries.\textsuperscript{114}

**Isoniazid**

Isoniazid, an anti-tubercular drug, is used alone or in combination with other drugs to eliminate the active (growing) bacteria. Usually, the therapy with isoniazid is continued for a longer time (6–12 months) since the bacteria may exist in a resting state for a longer period of time. The studies have indicated severe and fatal hepatitis with isoniazid therapy.\textsuperscript{114, 115} The frequency of hepatotoxic reactions are higher in aged patients over 65 years. Additionally, daily alcohol consumption increases the risk of hepatitis. In the patients receiving isoniazid, the symptoms of hepatic damage appear late, usually after 3 months of treatment.

In the liver, isoniazid is metabolized primarily by N-acetyl transferase 2 (NAT-2) to acetyl-isoniazid, which subsequently is converted to mono-acetyl hydrazine (MAH) and non-toxic diacetyl hydrazine, as well as other minor metabolites.\textsuperscript{114, 115} Studies have revealed that reactive metabolites of MAH are toxic to tissues due to ROS generation.\textsuperscript{116, 115} Isoniazid inhibits glutathione biosynthesis, activities of antioxidant glutathione peroxidase and catalase activity in rats.\textsuperscript{117, 118, 115} Furthermore, acetyl-hydrazine, a metabolite of isoniazid, causes damage to hepatic cells by covalently binding to liver macromolecules. In an epidemiological study, it has been reported that homozygous CYP2E1 c1/c1 host gene polymorphism, which results in enhanced CYP2E1 activity, causes higher risk of hepatotoxicity in patients.\textsuperscript{114, 115}
Pyrazinamide can cause a dose-dependent hepatotoxicity and should be used with added caution in patients on other anti-TB medications.[119-121]

**Nonsteroidal anti-inflammatory drugs**

NSAIDs are group of drugs which are widely used in general population and the possibility of hepatic injury was higher in individuals.[122] Diclofenac (by impaired hydroxylation) and sulindac (by hypersensitivity mechanism) are two NSAIDs causing more hepatotoxicity i.e., hepatocellular injury and cholestatic injury, respectively.[123, 124] In patients with end stage liver disease these drugs should not be used.[125] Patients with cirrhosis are at higher risk of aspirin induced hepatotoxicity due hypoalbuminaemia associated with liver disease.[126] It is known that use of aspirin in children are avoidable in febrile illness because of risk of Reye’s syndrome.[127] Small case series of 3 individuals reported that risk of hepatotoxicity was increased by ibuprofen in patients with chronic hepatitis C.[128] Another study conducted in Spain reported 421 ibuprofen induced liver injury cases.[129]

**Acetaminophen**

Paracetamol is commonly utilized analgesic-antipyretic drugs in population which relatively safe at recommended therapeutic doses.[130] It is associated with liver injury in major concern worldwide when used in high doses.[131-133] Acetaminophen is metabolized to N-acetyl-p-benzoquinoneimine by CYP enzymes, which is subsequently detoxified by reduced glutathione (GSH) to a threshold concentration, after which GSH depletion occur leading to the covalent binding of the metabolite to the macromolecules.[134, 135] Overdose of acetaminophen in animal model reported induction of massive necrosis however, only those hepatocytes undergo necrosis in acetaminophen-protein adducts formation occurs.[135]

**Herbal Medication used in management of drug induced hepatotoxicity**

Herbal antioxidants have attracted the researchers due to its potential and efficacy against drug-induced liver toxicity. Natural products used in China and India as traditional medicine for the treatment of liver disorders are of great interest in these days. These are the potential sources for new therapeutic agents that could be used in the prevention of hepatic injuries. Natural products rich in triterpenes, flavonoids or polyphenols, have been now established as powerful hepatoprotective agents in experimental liver-injury cell and animal models. The basis behind the protection provided by the natural products is hypothesized to be their antioxidant property through which they remove the free radicals from the cellular environment and therefore provide protection against ROS mediated damage to membrane
Additionally, the protective potential of natural products is also contributed by its interaction with various CYP isoforms, its capability to increase GSH biosynthesis, level of Phase II/antioxidant enzymes and to inhibit the entry of toxins to the body. Some of the natural products containing polyphenols are considered as potential chemopreventive and hepatoprotective agents. In the last decade, several studies have been conducted to investigate the mechanism of action of natural products at biochemical, genomic and proteomic levels. The most extensively investigated natural products for hepatoprotection are silymarin, resveratrol, curcumin and gingko due to their high efficacies, low or no toxicity and easy availabilities.

**Silymarin**

Silymarin, isolated from the seeds of milk thistle (Silybum marianum), it is an unique flavonoid complex with main constituents such as silybinin, silydianin and silychristin. Two main mechanisms of action of silymarin have been proposed based on its cell-regenerating function and cytoprotective effect. Cytoprotection is mediated by its antioxidant properties and direct interaction with cell membrane components. Silymarin has been also reported to have anti-inflammatory, anti-fibrotic and anti-proliferative effects. Diverse biochemical reactions, such as, the incitement of the synthetic rate of ribosomal RNA (rRNA) species through the induction of polymerase I and rRNA transcription, shielding the cell from free radical-mediated injury and blockage of the uptake of toxins, also contribute to the protective potential of silymarin. Silymarin offers protection against enlarged liver by inhibiting 5-lipoxygenase, production of leukotrienes and generation of free radicals in Kupffer cells. Moreover, silybin, a major component of silymarin, protects against the membrane lipid peroxidation and cellular damage in the mouse hepatocytes. Silymarin has low oral absorption, oral dosages of 420 mg/day have shown some therapeutic potential, with good tolerability in alcoholic cirrhosis patients. In a clinical trial with over 2000 patients with chronic liver diseases, administration of silymarin extract for 8 weeks resulted in a significant decrease in liver damage index in approximately 88% of the patients. It was remarkable that some minor side effects were observed only in less than 1% of patients.

**Resveratrol**

Resveratrol (trans-3,4′,5-trihydroxy-trans-stilbene) is a natural polyphenol present in significant amounts in peanuts, the skin of grapes and red wine. The substitution of the hydroxy with methoxy groups in resveratrol molecules may increase its lipophilicity and...
binding to the active sites of CYPs.\(^{[151]}\) Recently it has been shown by, that resveratrol prevents acetaminophen-mediated liver damage by inhibiting CYP-mediated bioactivation of acetaminophen and regulating SIRT1, p53, cyclin D1, and PCNA to facilitate liver regeneration.\(^{[152]}\) It was found that pre-treatment of resveratrol effectively reversed As\(_2\)O\(_3\)-induced liver toxicity indices and resulted in a significant improvement in hepatic function in cat models. Moreover, resveratrol also improved the glutathione levels, activities of antioxidant enzymes and attenuated As\(_2\)O\(_3\)-induced increases in reactive oxygen species and malondialdehyde production in liver tissues.\(^{[153]}\) Resveratrol has also been shown to offer protection against methotrexate and sodium fluoride induced hepatotoxicity in animal models.\(^{[154, 155]}\)

**Curcumin**

Curcumin is one of the most widely used herbal formulations to protect drug-induced toxicity. It is the major constituent of the spice turmeric extracted from the root of Curcumalonga Linn. It is metabolized to curcumin glucuronides, sulfates, tetrahydrocurcumin and hexacurcumin in the intestine and liver of human and rats and is reported to exhibit antioxidant, anti-inflammatory, choleric, anti-carcinogenic, antiviral, and anti-infectious activities.\(^{[156, 157]}\) It inhibits the expression of the enzyme cyclooxygenase 2 via interference with activation of the transcription factor NF-κB and is a potential hepatoprotectant.\(^{[158, 159]}\) Some study showed the curcumin-mediated protection against paracetamol-induced liver damage by restoring antioxidant activity of liver. They further showed that curcumin effectively restored the paracetamol-mediated increase in matrix metalloproteinase-8 (MMP-8), interleukin-1β (IL-1β), IL-8, tumor necrosis factor-α (TNF-α), and acute phase proteins and decrease in the expression of antioxidant genes.\(^{[160]}\) Curcumin offers hepatoprotection against cisplatin, alcohol and heavy metals-induced liver damage in animals.\(^{[160-162]}\)

**Gingko**

The Ginkgo biloba extract possess memory-enhancing, cognition-improving, immuno-modulating, apoptosis-inducing, and antiplatelet effects.\(^{[164]}\) The therapeutic benefits of this herbal medicine in neurological disorders, chronic refractory schizophrenia, hepatotoxicity, and in sleep disturbance of depressed patients have been reported.\(^{[164-166]}\) The major constituents of ginkgo include flavonoids (e.g., kaempferol), terpenoids (e.g., ginkgolides and bilobalides), and organic acids (e.g., ginkgolic acids and alkylphenols).\(^{[167, 168]}\) Intake of Ginkgo biloba extract may alter the hepatic metabolism by modulating hepatic drug
metabolizing enzymes, altering the level of antioxidant enzymes and endogenous antioxidants such as GSH. The altered hepatic metabolism may result in the clearance of co-administered drugs, in particular, that have reduced renal and liver function.\textsuperscript{169}

**CONCLUSION**

The nature and dose of a particular drug are not the only determining factors of cell injury. Other factors such as an individual's gene expression profile, antioxidant status and the capacity for regeneration are also crucial. Several mechanisms are involved in the initiation of liver cell damage and aggravate ongoing injury processes. Dysfunction of these vital cell organelles results in impairment of dynamic equilibrium in homeostatic condition, thus resulting in intracellular oxidative stress with excessive formation of reactive oxygen species. Major causes of the hepatotoxic reactions by drugs are elevated ROS generation, oxidative stress and suppressed immune responses. Hepatotoxicity remains a major cause of drug withdrawal from the market. Recent examples in the USA and Europe are ximelagatran, nefazodone, nimesulide, ebrotidine, trovafloxacin, troglitazone, bromfenac, and so forth. Natural products have shown great promise in combating against the toxicity of several commonly used drugs, including acetaminophen and paracetamol. Additionally, some of these natural products, such as resveratrol and curcumin, are now widely accepted chemopreventive agents. Due to easy availability and dietary nature, it is time to promote the natural products as supplementary medication with drugs that also cause toxicity to cells. Although a majority of natural products investigated to date are non-toxic, some studies have shown liver toxicity by certain natural products. Therefore, the proper selection of the natural products is also necessary. It is envisioned that natural products will not only lower the risk of drug-induced liver damage, but also provide an alternative solution to remedy the drug-induced hepatotoxicity.

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