INTRODUCTION
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 [3]. Hepatotoxicity refers to liver dysfunction, which is associated with certain medicinal drugs and chemicals. Medicinal drugs are converted into chemically reactive metabolites in liver, which have the ability to interconnect with cellular macromolecules such as protein, lipids and nucleic acids, leading to protein dysfunction, lipid peroxidation [LPD], DNA damage and oxidative stress in liver. This damage of cellular function can disintegrate in cell death and likely liver damage. More than 900 drugs have been implicated in causing liver injury and it is the most common reason for a drug to be withdrawn from the market. More than 75% of idiosyncratic drug reactions result in liver transplantation or death [2]. Liver plays a pivotal role in regulating various physiological processes [3]. These hepatotoxic agents activated some enzymes activity in the cytochrome p-450 system such as CYP2E1 that also leads to oxidative stress. Injury to hepatocyte and bile duct cells lead to accumulation of bile acid inside liver leads to promote further liver damage. Damaging hepatocyte results in the activation of innate immune system like Kupffer cells (KC), natural killer (NK) cells, and NKT cells, which will be useful in understanding their impact on human health. However, the experimental model is a roadmap for discovery of new molecular, noble signaling pathways for the betterment of human race [6,7].

Paracetamol induced hepatotoxicity
Paracetamol, a widely used analgesic and antipyretic drug, produces acute liver damage in high doses. Paracetamol administration causes necrosis of the centrilobular hepatocytes characterized by nuclear pyknosis and eosinophilic cytoplasm, followed by large excessive hepatic lesion. The covalent binding of N-acetyl-p-benzoquinoneimine, an oxidative product of paracetamol to sulfydryl groups of protein, result in lipid peroxidative degradation of glutathione (GSH) level and thereby, produces cell necrosis in the liver [8,9]. Hepatotoxicity was noted after administration of paracetamol (500 mg/kg, orally) for 2 weeks in rats [10].

Galactosamine induced hepatotoxicity
Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylic nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in the cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. This mechanism of toxicity brings about an increase in the cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylic nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in the cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes. Galactosamine produces diffuse type of liver injury simulating viral hepatitis. It presumably disrupts the synthesis of essential uridylic nucleotides resulting in organelle injury and ultimately cell death. Depletion of those nucleotides would impede the normal synthesis of RNA and consequently would produce a decline in protein synthesis. This mechanism of toxicity brings about an increase in the cell membrane permeability leading to enzyme leakage and eventually cell death. The cholestasis caused by galactosamine may be from its damaging effects on bile ducts or ductules or canalicular membrane of hepatocytes.
Thioacetamide induced hepatotoxicity

Thioacetamide interferes with the movement of RNA from the nucleus to the cytoplasm which may cause membrane injury. A metabolite of thioacetamide (perhaps s-oxide) is responsible for hepatic injury. Thioacetamide reduce the number of viable hepatocytes as well as rate of oxygen consumption. It also decreases the volume of bile and its content, i.e. bile salts, cholic acid and deoxycholic acid. Thioacetamide is oxidized to a reactive metabolite S-oxide which is responsible for the amending in cell permeability and the concentration of Ca++ increases intracellular in nuclear volume and also obstructs mitochondrial function which clues to cell death [12]. Administration of thioacetamide (200 mg/kg, i.p) thrice in a weekly for 8 weeks to induced hepatotoxicity [11].

Carbon tetrachloride (CCl₄) induced hepatotoxicity

CCl₄ is metabolized by CYPs in endoplasmic reticulum and mitochondria with the formation of CCl₃O⁻, a reactive oxidative free radical, which initiates lipid peroxidation. Administration of a single dose of CCl₄ to a rat produces, within 24 hrs, a centrilobular necrosis, and fatty changes. The poison reaches its maximum concentration in the liver within 3 hrs of administration. Thereafter, the level falls and by 24 hrs there is no CCl₄ left in the liver. The development of necrosis is associated with leakage of hepatic enzymes into serum [3]. It has been noted that administration of dose of 2 (ml/kg, S.C) of CCl₄, for 2 days in rats showed significant alterations in serum glutamic pyroic transaminase (SGPT), serum glutamic oxalacetic transaminase (SGOT) levels which leads to hepatotoxicity [14].

Lead induced hepatotoxicity

Many metals play important roles in the functioning of the enzyme, cell-signaling processes and gene regulation. Lead is a blue-gray and highly toxic divalent metal that occurs naturally in the earth’s crust and is spread throughout the environment by various human activities. Lead induced hepatic damage is mostly rooted in LPO and disturbance of the pro-oxidant antioxidant balance by generation of reactive oxygen species (ROS) [15]. Lead toxicity lead to free radical damage by two separate pathway: (1) Generation of ROS, including hydro-peroxides, singlet oxygen, and hydrogen peroxide and, (2) the direct depletion of antioxidant reserves. The cell membrane is the main target of the oxidative damage produced by heavy metals. This is mainly due to changes in polyunsaturated fatty acids having double bonds, largely present in the phospholipids of membranes. Lead is known to produce oxidative damage by enhancing peroxidation of membrane lipids, and LPO is a deleterious process carried out by free radicals. LPO is an outcome of the chain of events involving initiation, propagation, and termination reactions. GSH depletion is another important mechanism of lead toxicity. GSH is a tri-peptide containing cysteine and termination reactions. GSH depletion is another important mechanism of lead toxicity. GSH is a tri-peptide containing cysteine and thiol groups and reductive potency. It can act as a non-enzymatic antioxidant by direct interaction of the –SH group with ROS, or it can be involved in the enzymatic detoxification reaction for ROS as a cofactor. Lead binds exclusively to the –SH group, which decreases the GSH level and can interfere with the antioxidant activity of GSH [16]. Rats administered a single dose (20 mg/kg, i.p) of lead acetate revealed significant elevations of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), aspartate transpeptidase, a membrane bound enzyme in serum. Ethanol inhibits GSH peroxidase, decrease the activity of catalase, superoxide dismutase, along with an increase in levels of GSH in liver. The decrease in activity of antioxidant enzymes superoxide dismutase, GSH peroxidase are speculated to be due to the damaging effects of free radicals produced following ethanol exposure or alternatively could be due to a direct effect of acetaldehyde, formed by oxidation of ethanol [20]. It has been observed that the dose of alcohol (5 ml/kg, orally) for a period of 4 weeks and increase in serum levels of ALT and AST which leads to liver damage in rats [10].

Anti-tubercular drugs induced hepatotoxicity

Drug-induced hepatotoxicity is a potentially serious adverse effect of the currently used anti-tubercular therapeutic regimens containing isoniazid (INH), rifampicin and pyrazinamide. Adverse effects of anti-tubercular therapy are sometimes potentiated by multiple drug regimens. Thus, though INH, rifampicin and pyrazinamide each in itself are potentially hepatotoxic, when given in combination, their toxic effect is enhanced. INH is metabolized to monoacetyl hydrazine, which is further metabolized to a toxic product by CYP450 leading to hepatotoxicity. Patients on concurrent rifampicin therapy have an increased incidence of hepatitis. This has been postulated due to rifampicin-induced CYP450 enzyme-induction, causing an increased production of the toxic metabolites from acetetyl hydrazine (AcHz). Rifampicin also increases the metabolism of INH to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half-life of AcHz (metabolite of INH) is shortened by rifampicin and AcHz is quickly converted to its active metabolite by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and rifampicin in combination. Rifampicin induces hydrolysis pathway of INH metabolism into the hepatotoxic metabolite hydrazine. Pharmacokinetic interactions exist between rifampicin and pyrazinamide in tuberculosis patients, when these drugs are administered concomitantly. Pyrazinamide decreases the blood level of rifampicin by decreasing its bioavailability and increasing its clearance. Pyrazinamide, in combination with INH and rifampicin, appears to be associated with an increased incidence of hepatotoxicity [21]. The combined administration of the INH and rifampicin at the dose (50 mg/kg, orally) for 28 days caused hepatotoxicity in rats [22].

Azathioprine (AZA) induced hepatotoxicity

AZA is an important drug used in the therapy of autoimmune disorder and in preventing graft rejection. The nitro-conjugated double bond of
imidazole ring of AZA is a Michael acceptor. AZA is cleaved in vitro to 6-MP non-enzymatically by a nucleophilic attack of sulfhydryl groups primarily GSH, on the b carbon in the activated double bond AZA toxicity to rat hepatocytes was preceded by depletion of GSH. Prior GSH depletion enhanced toxicity while supplemental GSH was protective. In hepatocytes, GSH is consumed during metabolism of AZA to 6-MP. The mechanism of AZA toxicity to mitochondrial injury with profound depletion of ATP and cell death by necrosis. Lipid peroxidation as well as altered levels of some endogenous scavengers is taken as indirect in vivo reliable indices for the contribution of free radical generation and in turn oxidative stress [23]. It has been reported that the administration of AZA (1.5 mg/kg orally) for 4 weeks induced hepatotoxicity in rats [24].

Lithocholic induced hepatotoxicity

The mechanism of the hepatobiliary injury in the lithocholic acid (LCA) progressively used model of cholestatic liver injury. The etiology of LCA induced cholestasis in the rat includes biochemical alterations of the bile canalicular membrane. Due to the poor solubility of LCA the crystalline plugs develop in bile canaliculi and impaired filtering. Administration of LCA can outcome in hepatocellular necrosis with significant reductions in basolateral bile acid uptake and sinusoidal bile acid efflux transporters (Mrp3) increased. These changes in the liver represent an inherent toxicity of accumulating bile acids. The administration of LCA (4 µmol/kg, I.V., single dose) developed hepatotoxicity in rats [25].

Cadmium-induced hepatotoxicity

Cadmium metals and metalloids affect almost every organ of the body, including the liver. One such metal is cadmium, which is of concern because of its increasing prevalence as an environmental contaminant [26]. Prolonged exposure to cadmium results in injury to the liver. A large bolus dose of cadmium causes injury to a number of tissues, including the liver [27]. Cadmium induces oxidative damage in different tissues by enhancing per-oxidation of membrane lipids in tissues and altering the antioxidant systems of the cells. The per-oxidative damage to the cell membrane may cause injury to cellular component due to the interaction of metal ions with the cell organelles [28]. Cadmium toxicity leads to enhanced production of ROS such as superoxide ions, hydroxyl radicals, and hydrogen peroxides. These ROS result in increased lipid per-oxidation, hepatic congestion, ischemia and hypoxia [29]. The resultant ischemic hypoxia leads to neutrophil infiltration, KC activation, and inflammation, which could potentially contribute to the widespread hepatocellular apoptosis and necrosis [30]. Cadmium causes increase in serum concentrations of urea, creatinine, glucose, AST, acid phosphatase, alkaline phosphatase, alanine transaminase, aspartate transaminase, and serum bilirubin whereas reducing serum protein and tissue protein concentration. It has been noted that administration of cadmium with dose (1 mg/kg, orally) for 15 days in rats showed increased levels of acid phosphatase, which leads to liver tissue damage [31].

Alyl alcohol-induced hepatotoxicity

The toxicity of allyl alcohol is considered to be mediated via acrolein, which is generated from allyl alcohol by the enzyme alcohol dehydrogenase [32]. Acrolein is a powerful electrophile and reacts with nucleophiles such as sulfhydryl groups [33]. The reaction is accelerated by the activity of cytosolic GST to form an aldehyd e-GSH adducts, which are metabolized to acrylic acid [34]. GST is primarily involved in the reaction, which result in a depletion of cellular GSH stores, followed by hepatocellular necrosis [35]. Allyl alcohol induces increase in SGOT, SGPT and total bilirubin, whereas decrease in total protein. The rats treated with allyl alcohol shows necrosis around branches of the central hepatic vein and presence of a large amount of nuclear debris. It has been noted that the administration of a single dose (35 mg/kg, i.p.) of allyl alcohol in rats leads to increased liver weight associated with moderate-to-severe hepatocellular necrosis [36].

Halothane induced hepatotoxicity

Halothane is chemically 2-bromo-2-chloro-1,1-trifluoroethane. It has been used widely as an inhaled anesthetic and as liver toxicant in animal models [37]. It is well established that halothane is metabolized in the liver as a lipophilic xenobiotic to hepatotoxic intermediates by monoxygenases through the CYP450-2E1 system [38]. Thus, halothane anesthesia causes hepatocellular necrosis, destruction of the lipid-protein interactions in human erythrocyte membranes, decrease in activities of membrane enzymes and alteration of cerebral glucose-6-phosphate dehydrogenase activities [39]. Halothane treated rat liver shows extensive peribiliary necrosis and denaturation. Administration of halothane at dose (30 mmol/kg, i.p.) dissolved in 2 ml of olive oil to female, and male rats lead to hepatotoxicity at 12 hrs after the administration of drug [40].

Aflatoxin B1 (AFB1) induced hepatotoxicity

AFB1 is a naturally occurring fungal toxin that causes both acute hepatotoxicity and liver carcinoma in humans and animals. AFB1 produces the hepatotoxicity through the formation of adducts with DNA, observed both in vitro and in rat liver [41]. These adducts are derived from highly reactive eco-epoxide metabolites of AFB1, as a result of oxidation reactions within the liver [42]. Several cytochromes P450 have been implicated in this activation and in human these were identified as CYP1A2 and CYP3A4 [43]. Acute toxicity was initially attributed to mainly genotoxic effects of the epoxide; dependent on the formation of DNA adducts, which at high levels lead to cell death. However, a dialdehyde metabolite of AFB1 that rapidly forms from the epoxide, can form adducts with proteins, and these were proposed to contribute to the acute toxicity [44]. In addition, such cellular necrotic damage caused by AFB1 dialdehyde may lead to compensatory liver hyperplasia and by so doing may promote the incorporation of mutations into the DNA of dividing cells and contribute towards carcinogenicity initiated by the AFB1-eco-epoxide [45]. AFB1 increases serum concentrations of SGOT, SGPT, alkaline phosphatase and bilirubin, and decrease in serum cholesterol. The prominent gross pathologic and histopathologic changes in the liver are hemorrhage, necrosis, and massive accumulation of lipid. Rats treated with single dose (1 mg/kg, orally) of aflatoxin developed significant liver damage due to increased activities of SGOT, SGPT and ACP in serum [46].

Ranitidine induced hepatotoxicity

Liver injury induced by ranitidine is due to its metabolite which may lead to hepatic oxidative damage, and one of its metabolite is generating the immunological reaction. It also produces a reaction as reflected by induction of hepatocytosis. Severe inflammatory changes with collagenous septa beginning to form after pronounced centrilobular and bridging necrosis. In the parenchyma, there was focal liver cell necrosis with some accumulation of histocytic elements and slight steatosis and cholestasis. Portal tract shows fibrosis, bile duct proliferation and infiltrate consisting of lymphocytes, plasma cells, polymorphs, and eosinophils. Liver injury is manifested in terms of increase in levels of serum aminotransferases, most hepatic inflammation by both lymphocytes and eosinophils and slight focal hepatocellular necrosis also causes liver cholestasis associated with increased plasma bilirubin and alkaline phosphatase [47]. Administered ranitidine for 24 hrs at dose (30 mg/kg, iv) leads to hepatotoxicity in rats increases in serum ALT and serum AST activity. These changes reflect hepatotoxicity in rats [48].

Mercury induced hepatotoxicity

Human activities play a major role in polluting the environment by toxic and carcinogenic metal compounds. These are evidences that these metals by accumulating contaminate waters sources and food chain with their compounds. Mercury and its compounds are widely used in industries, and their hazards to animals have been documented. Mercury is a transition metal, and it promotes the formation of ROS such as hydrogen peroxides. These ROS enhance the peroxides and hydroxyl radicals. These lipid peroxides and hydroxyl radical may cause cell membrane damage and thus destroy the cell. Mercury also inhibits the activities of the free radical quenching enzyme such as catalase, superoxide dismutase, and GSH peroxidase. Mercury causes cell membrane damage like lipid per-oxidation, which leads to the...
imbalance between synthesis and degradation of enzyme protein. The excess production of ROS by mercury may be explained by its ability to produce alteration in mitochondria by blocking the permeability transition pore [49]. It has been noted that after the administration of mercuric chloride (5 mg/kg, ip.) for 20 days and (2 mg/kg, orally) for 30 days induced hepatotoxicity in rats [50].

**Hormones induced hepatotoxicity**

Although many new agents are now available, androgens are still used in the hormonal manipulation of breast cancer and carry the risk of intrahepatic cholestasis [51]. The chronic use of any 17-alkyl androgen has the potential for the development of hepatic adenocarcinomas [52,53]. Cholestatic hepatitis, likely idiosyncratic, has been reported following the use of the anti-androgen flutamide for prostate cancer [54], megestrol acetate and tamoxifen therapy for breast cancer [55,56]. It has been observed that the rats administered tamoxifen (45 mg/kg/day, ip.) in 0.1 ml of dimethylsulfoxide and normal saline for 6 days induced hepatotoxicity [57].

**Phalloidin induced hepatotoxicity**

Phalloidins such as phallolidin are toxic cyclic peptide compounds produced by the green death cup of mushroom Amanita phalloides [58]. Phalloidins are belonging to the class of bicyclic peptides with a transannular thioether bridge. Their intoxication mechanism in the liver involves a specific binding of the toxins to F-actin that, consequently, prevents the depolymerization equilibrium with G-actin [59]. It induces hepatotoxicity in rats at an intravenous dose of 50 g/100 g body weight phallolidin also induces a cytolytic lesion. Phallolidin causes severe liver damage characterized by marked cholestasis, which is due in part to irreversible polymerization of actin filaments [60].

**Acryl amide (AA) induced hepatotoxicity**

AA is a water-soluble vinyl monomer used in the production and synthesis of polycrylamides. Monomeric AA has been shown to cause diverse toxic effects in experimental animals. AA is carcinogenic to laboratory rodents and is described by the International Agency for Research of Cancer as a probable carcinogen to humans. The human body, AA is oxidized to the epoxide glycidamide (2, 3-epoxypyrrolidinamide) via an enzymatic reaction involving CYP4502E1. AA undergoes biotransformation by conjugation with GSH and is probably the major route of detoxification. Rats were treated daily with AA at dose (6 mg/kg, ip.) for 15 days leads to hepatotoxicity [61].

**Microcystin induced hepatotoxicity**

Microcystin-LR, a cyclic heptapeptide synthesized by the blue-green algae, microcystis aeruginosa, is a potent hepatotoxin. Pathological examination of livers from mice and rats that received microcystin-LR revealed severe, paracentral, diffuse, centrilobular hepatocellular necrosis, and hemorrhage. Mice receiving sub-lethal doses of microcystin (20 g/kg) for 28 weeks developed neoplastic liver nodules [62].

**Adriamycin induced hepatotoxicity**

Adriamycin (doxorubicin) is an antibiotic isolated from Streptomyces peucetius var Casius. Adriamycin is considered to be one of the most compelling drugs against a wide range of tumors. However, its clinical potential is contraindicated due to severe cytotoxic side effects Based on in vitro model of toxicity using isolated hepatocytes and liver microsomes, adriamycin has been shown to undergo redox cycling between semiquinone and quinone radicals during its oxidative metabolism. It has been noted that a single dose of adriamycin (10 mg/kg) induced hepatotoxicity in rats [63].

**Alpha-naphthylisothiocyanate (ANIT) induced hepatotoxicity**

ANIT injures bile duct epithelium and hepatic parenchymal cells in rats. It is commonly believed that ANIT undergoes bioactivation by hepatic, CYP450-dependent mixed-function oxidases. Rats administered once with ANIT at dose (75 mg/kg, ip.) show liver cell damage and biliary cell damage with cholestasis at 24 hrs, but not at 12 hrs, after ip. administration of ANIT [64].

**REFERENCES**