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Review Article

Different Experimental Models for Hepatotoxicity; A Review

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ABSTRACT

Medication and substance-induced liver damage stands among the main reasons drugs get withdrawn from distribution which potentially requires liver transplantation and leads to fatal consequences. This assessment describes the biological processes used by liver-damaging drugs to harm liver tissue and demonstrates the vital role which experimental animal testing plays in studying this pathology. The research explains that drug-induced reactive metabolites cause hepatotoxicity through their specific interactions with biological substances which trigger oxidative stress while promoting both inflammation and apoptosis processes. These mechanisms require study to uncover new therapeutic targets which will help enhance clinical hepatotoxicity management.

INTRODUCTION

Hepatotoxicity refers to liver damage caused by various drugs and substances. Drugs often result in chemically reactive metabolites upon liver metabolism that are able to correspond with proteins, lipids, and nucleic acids, among others of cellular composition. The interaction could result in protein malfunction, lipid peroxidation ,genetic mutation, and antioxidant depletion in the hepaatic organ, leading to cellilar apoptosis and hepatic injury. More than 900 drugs have been linked to hepatic system damage, making it a main factor for drugs being removed from the market. Additionally, over 75% of unpredictable drug-induced liver reactions lead to liver transplants or death[1].Glycogenosis, breakdown of erythrocytes, blood protein synthesis, endocrine synthesis, as well as toxic drug fumigate are some of the essential functions the liver undertakes in metabolism[2]. Injury to bile duct cells and hepatocytes causes the amassment of bile acids within the liver, worsening liver damage. Cytochrome P450 system enzymes like CYP2E1 are also activated by hepatotoxic chemicals, further contributing to oxidative stress. The natural immune response, comprising liver macrophages, natural killer (NK) cell, and natural killer T cells, is triggered by this hepatocellular injury. This leads to the release of inflammation-promoting

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molecules like IL-1 beta, gamma-interferon and TNF-alpha, which increase liver damage.In addition, many hepatotoxic agents damage mitochondria, the cellular organelles responsiblefor energy production. When mitochondria are damaged, hepatocellular injury results in necrosis or apoptosis, which is frequently mediated by signaling pathways initiated at the cell membrane, for example, death receptor pathways[3].To identify potential drug targets for liver damage, hepatotoxicity is induced in a range of experimental models. This review examines the different animal models developed to study hepatotoxicity and how they assist us in understanding the mechanisms of liver damage.

Drugs Which Causes Hepatotoxicity

1. Acetaminophen (Paracetamol)

One of the commonest analgesics, acetaminophen, can lead to liver toxicity upon overdose. The metabolism of acetaminophen leads to N-acetyl-p-benzoquinone imine (NAPQI) formation as a reactive intermediate which binds to the cellular proteins and depletes glutathione stores, contributing to oxidative stress and hepatocellular necrosis. Impact on Clinical Practice: Even quite small amounts of overdose can lead to acute liver failure, which will require, immediate medical intervention, suchas glutathione repletion with N-acetylcysteine therapy.[4]

2. Nonsteroidal anti-inflammatory Drugs (NSAIDs)

NSAIDs like ibuprofen, diclofenac, and naprosyn are generally linked to liver injury. Both doserelated and idiosyncraticliver injury can be caused by them. The most common mechanism of NSAID-induced hepatotoxicity is the prevention of the cyclooxygenase(COX) catalysts, which leads to the accumulation of reactive metabolites and liver injury. Impact on Clinical Practice: While chronic use or overdosing is likely to lead to liver injury, which may vary from mild transaminitis to sudden liver failure, acute liver injury is quite rare.[5]

3. Methotrexate

Methotrexate is a chemotherapeutic and immunosuppressive drug that may be hepatotoxic, especially when employed long term. Since dihydrofolate reductase is inhibited, toxic substances like polyglutamates accumulate and harm liver cells with oxidative damage and fibrosis. Clinical Impact: Cirrhosis and liver fibrosis may follow chronic administration. Follow-up of patients receiving methotrexate treatment needs periodic liver function tests.[6]

4. Isoniazid

An antibiotic isoniazid is commonly prescribed to treat tuberculosis. Its metabolism by the liver can cause oxidative stress and liver injury and also yield toxic metabolites that can deplete cellular antioxidants such as glutathione.

Clinical Impact: Hepatitis caused by isoniazid can be idiosyncratic or dose-dependent. In rare cases, acute liver failure can occur.[7]

5. Statins

To lower cholesterol, statins are often prescribed. Through inhibition of the HMG-CoA reductase enzyme, they may cause hepatotoxicity by promoting the accumulation of toxic intermediates. While statin-induced liver injury is generally trivial, it may on occasion lead to elevated liver enzymes and true liver injury.

Clinical Impact: Even though hepatotoxicity is often asymptomatic, statin patients should undergo

routine liver function tests, particularly if they have symptoms of liver disease.[8]

6. Antiepileptic (e.g, Phenytoin, Valproate)

Phenytoin and valproate, two drugs prescribed for the treatment of epilepsy, are capable of causing liver damage in susceptible individuals. Phenyltoin can generate reactive oxygen species (ROS), while valproate is metabolized to toxic metabolites that interfere with mitochondrial function.

Clinical Impact: Hepatotoxicity, particularly in children and patients with pre-existing metabolic disorders, may range from mild elevations in liver enzymes to extreme liver decompensation.[9]

7. Herbal Supplements (e.g, Kava, Comfery and Chaparral)

A number of herbal supplements have been linked to hepatotoxicity, including kava, which can cause acute liver failure through its action on hepatic enzymes and mitochondrial dysfunction, comfrey, which contains pyrrolizidine alkaloids that are hepatotoxic, and chaparral, which may cause damage through its reactive metabolites.

Clinical Implication : Herbals are being used regularly in ignorance of the possible toxic impact, and hepatotoxicity could be potent with acute liver failure in severe situations.[10]

Experimental Models for Hepatotoxicity

Liver toxicity caused by the drug is the primary source of drug detoxification and clinical failure and is characterized in large measure through the application of animal models.[11] Animal models allow us to develop a better appreciation of the underlying of drug stimulated hepatotoxicity. Thus, free radical damage, inflammation, mitochondriopathy, and apoptosis represent some of the mechanisms by which hepatotoxic drugs damage the liver. By making it possible for researchers to visualize the molecular and cellular changes caused by drug exposure, animal studies facilitate the identification of these pathways. These pathways are often investigated in rodent models (e.g., rats and mice), which assist in the identification of key hepatotoxic agents.[12] Very early on in the drug research stage, animal models help identify harmful liver effects. For example, drugs such as isoniazid and acetaminophen have been extensively studied in rodent models, which have indicated the damage that these drugs cause to the liver and helped forecast the risk of liver damage in humans.[13] Whole-animal systems for in vivo tracking are complex. The compounds target cells sequentially—first through direct exposure, then through absorption, metabolism, diffusion, and elimination. The order of these events and the way the whole animal exposes its cells in an organ-specific manner create an in vivo system that serves as a roadmap for the human condition. In terms of conducting relevant clinical experiments to study the hepatic toxicity of new compounds, whole-animal systems can darn near duplicate the human peril in tracking pathway discovery. Small animal models like those of rats and mice used in basic experiments may lead to understanding how mechanism action affects organs and can help detect human health issues associated with widespread cellular vulnerability. Properties of molecules that make paths by way of cellular signaling or go off road help us understand the models better. So, next time you come across an animal experiment, consider it a potential precursor for 'molecular pathology' in human health.[14]

Thioacetamide induced Hepatotoxicity

Similar to CCl4, thioacetamide is an organosulfur compound utilized in models of chronic and acute liver damage. TAA undergoes two steps of activation within the liver: the first conversion of TAA into thioacetamide-S-oxide (TASO) is carried out by cytochrome P450s or flavin adenine dinucleotide (FDA) containing mixed function oxygenase, with subsequent metabolism into thioacetamide-S,S-dioxide (TASO2).[15]

Metabolism and toxicity mechanism

S-oxide of thioacetamide (TASO) and S,S-dioxide of thioacetamide (TASO2) are toxic metabolites formed when TAA undergoes oxidative bioactivation in rats. Liver injury ensues as a consequence of these metabolites' interaction with proteins and lipids. Surprisingly, minimal damage is seen in rat hepatocytes exposed directly to TAA alone. However, TASO alone is very toxic, suggesting that it is an essential part as a toxic intermediate. Some of the toxic effects observed in vivo can be attributed to the mechanism by which TASO is converted back to TAA and redox cycling. In laboratory animals, especially rats, thioacetamide (TAA) is most often used to induce acute and long term liver toxicity to study the mechanisms of liver injury [15]. Thioacetamide (200 mg/kg dose, i.p. route) was given thrice a week for eight weeks to induce hepatotoxicity.[16] An overdose of a single large thioacetamide dosage leads to acute hepatotoxicity, when the liver metabolizes it to form reactive metabolites like thioacetamide S-oxide (TASO). The metabolites lead to oxidative stress, peroxidation of lipids, and cell damage, which increases blood liver enzymes like ALT and AST and results in inflammation and hepatocellular necrosis. Acute liver damage can be detected by histopathological examination, which shows localized necrosis of hepatocytes and ballooning degeneration. In contrast, repeated and prolonged administration of small doses of TAA leads to chronic hepatotoxicity and aggravates liver damage with passage of time. Cirrhosis and liver fibrosis are the outcomes of prolonged dosing, and hepatocellular carcinoma may later arise. Oxidative stress is a dominant component in both acute and chronic models, and anti-inflammatory or antioxidant treatment modalities are often tried to reduce liver damage. TAA-induced liver damage models are helpful for evaluating potential hepatoprotective therapies and for understanding the pathophysiology of liver diseases. [15]

Paracetamol induced Hepatotoxicity

Over-the-counter paracetamo (acetaminophen), is a popular analgesic and antipyretic medication. While therapeutic doses are considered safe, acute hepatotoxicity (liver damage) may occur from overdose or chronic high dose administration. Paracetamol-induced hepatotoxicity is a severe risk because it may result in instant hepatic damage and, in extreme cases, require a liver transplant.[17]Acetaminophen-induced toxicity mechanism is comprehensively analyzed. In brief, toxicity develops when too much dosages of acetaminophen cause metabolic activity through a subsidary pathway regulated by the cytochrome P450 enzyme family. N-acetyl-p-benzoquinone imine (NAPQI), a hepatotoxic metabolite formed by this pathway, is assumed to exert hazardousness mainly through the generation of protein adducts in mitochondria and formation of ROS.[18] The oxidative product of tylenol, acetaminophen reactive metabolite, binds covalently with the sulfydryl protein groups, leading to oxidative breakdown of lipids and subsequent liver parenchymal cell death [19,20]. During the investigation of the hepatotoxicity of paracetamol, rodent models are used most often. Large amounts of paracetamol are commonly administered to rats and mice in an attempt to induce hepatic injury,

which is characterized by oxidative stress, inflammation, hepatocellulae necrosis, and elevated liver enzymes (e.g., ALT and AST). Comparable pathophysiologic changes, including the generation of NAPQI, depletion of glutathione, and resultant oxidative damage to hepatocytes, are routinely seen in these animals after a paracetamol overdose in humans [21]. Following administration of 500 mg/kg of paracetamol orally twice a week, hepatotoxicity was noticed [22].

Alcohol induced hepatotoxicity

The hepatotoxic effects of ethanol have the ability to lead to cirrhosis, hepatitis, and fatty liver because the liver is very sensitive to them. Alcohol displaces fatty acids in the mitochondria, leading to fatty infiltration, which is reversible. However, since chronic alcohol consumption enhances fat oxidation during ethanol metabolism in the microsomal system, it can lead to cirrhosis and hepatitis. Alcohol consumption also leads to peroxidation of lipids, which damages membrane integrity and disrupts cellular functions, altering the fluidity and phospholipid composition of the membrane of the liver. Ethanol also enhances the liver's ethanol oxidation, which generates more free radicals and elevates the blood concentration of the membrane-attached enzyme glutamyl transpeptidase.Ethanol diminishes the activity of oxidative stress-reducing enzymes such as catalase and antioxidant enzyme superoxide scavenger and suppresses peroxidase enzyme with glutathione (GSH peroxidase) activity. Decreased activity of these enzymes has been thought to be the result of either direct acetaldehyde toxicity, a metabolite of ethanol oxidation, or oxidative damage from free radicals generated during ethanol metabolism [23].Studies have shown that rats given an oral dose of alcohol at 5 ml/kg, administered over four weeks have increased serum concentrations of ALT and AST, which cause liver damage [22].

Galactosamine induced liver injury

It is widely used experimental model for studying the mechanisms of hepatic dysfunction. The liver serves as the main location for galactosamine (GaIN) metabolism. a toxin sugar analog that inhibits RNA synthesis by blocking the synthesis of uridine monophosphate (UMP). Especially in hepatocytes, this inhibition causes cellular dysfunction and liver cell necrosis. Since GalN generates oxygen rasical that trigger fatty acid oxidation and other harm to plasma lipid layers and organelles, such as mitochondria, its toxicity is often associated with oxidative stress. By releasing pro-inflammatory cytokines and activating caspases, GalN also induces inflammation and the induction of apoptotic pathways. The model is also employed to examine the effect of glutathione depletion since revelation to GalN has been proven to significantly decerease the glutathione content of the liver, exacerbating free radical damage. This hepatotoxicity model is often employed to evaluate potential treatment compounds that attempt to counteract liver damage, including anti-inflammatory drugs and antioxidants. An intraperitoneal (IP) dose of 700–1,000 mg/kg of galactosamine is commonly adequate to induce liver damage. RNA synthesis of hepatocytes is altered by galactosamine, producing cell apoptosis and necrosis. The centrilobular region of the liver is where hepatocellular damage primarily occurs[24].

Carbon tetrachloride (CCL4) induced hepatotoxicity

Among the most frequent model systems for hepatic damage is the carbon tetrachloride (CCl_4)-induced hepatotoxicity system, which serves to study hepatocyte necrosis, inflammation, oxidative stress, and fibrosis of the liver. CCl_4 is biotransformed by the liver cytochrome P450 (CYP450) enzyme structure to create the highly

reactive trichloromethyl radical (CCl_3). Lipid peroxidation and malondialdehyde (MDA) formation are consequences of such radical interactions with cellular components, particularly lipids, that further damage liver cells. The resulting oxidative stress is a causative factor in inflammation, fibrosis, and hepatocellular injury. Activation of stellate cells is yet another action of CCl_4 leading to collagen deposition, fibrosis of the liver, and ultimately cirrhosis [25]. Within 24 hours after injection of a single dose of CCl4 in rats, the animal is affected by lipid changes and centrilobular necrosis. The toxin attains the peak levels in the liver within three hours. Within a day, the level falls and the liver has no trace of CCl4. Hepatic enzyme spilling into the serum is associated with the development of necrosis [26]. Increased AST and ALT serum levels have been seen in rats administered a subcutaneous dose of 2 ml/kg CCL4 for two consecutive days and it caused hepatotoxicity[27] Centrilobular necrosis, often demonstrated in histological studies, is one of the hepatotoxic effects of CCl_4. Increased concentrations of liver enzymes like ALT and AST are also linked to this condition. The model caused by CCl_4 is widely applied to investigate the molecular mechanisms of liver damage and regeneration and also to evaluate the effect of fibrosis-modifying treatment, antioxidants, and anti-inflammatory drugs [25]

Ranitidine induced hepatotoxicity

Ranitidine leads to liver injury due to its metabolites, one of which is inducing an immunoallergic response and the other of which can lead to hepatic oxidative injury. It also leads to a response, which is evidenced by hepatocyte infiltration. Extensive centrilobular and bridging necrosis, then extensive inflammatory changes and collagenous septa formation. Superciliary liver cell necrosis within the parenchyma and a small degree of histocytic element deposition, mild fatty change, and cholestasis were noted. Fibrotic change, biliary duct enlargement, and portal tract penetration with white blood cells, B cells, acidphils are all noted. Increased activity of transaminases, light infiltration of liver by eosinophils and immunocytes, and mild localized hepatocellular necrosis are all indications of liver damage. Liver cholestasis is also associated with increased plasma alkaline phosphatase and plasma bilirubin [28]. Rats receiving intravenous ranitidine 30 mg/kg for 24 hours develop hepatotoxicity as evidenced by elevated . Serum liver enzyme (ALT and AST) levels. Rat hepatotoxicity is indicated in these changes [29]

MSG Induced liver injury

Monosodium glutamate (MSG)-induced hepatotoxicity is a well-consolidated model to study the injury inflicted to the liver by excess glutamate intake. Excess doses of MSG, usually consumed orally, have been shown to cause considerable oxidative stress to liver cells in experimental animal studies. The main reason for the toxicity is the reactive oxygen species (ROS) formed upon metabolism of MSG that induce lipid peroxidation, glutathione (GSH) loss, and membrane damage. The concentration of liver enzymes in serum like ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are elevated, showing oxidative damage that results in hepatocyte necrosis, fatty infiltration, and liver impairment. When histologically liver tissues are inspected, hepatocellular damage and inflammatory infiltration are often seen. Through causing collagen deposition and activation of hepatic stellate cells, long-term high levels of MSG exposure can also be a causative factor in cirrhosis and fibrosis. The model is useful in evaluating potential hepatoprotective agents, such as anti-

inflammatory and antioxidant chemicals, to reduce the harm that glutamate toxicity inflicts on the liver. Since oxidative stress is harmful to mitochondrial function, which worsens liver damage, research has also established that mitochondrial dysfunction could be a contributor to MSG-induced hepatotoxicity[30]

Tunicamycin-induced hepatotoxicity

The well-known model of tunicamycin-induced hepatotoxicity is used to evaluate the effects of endoplasmic reticulum (ER) stress on liver physiology. The high-affinity glucosamine analogue tunicamycin suppresses the function of uridine diphosphate N-acetylglucosamine: dolichol N-acetylglucosamine kinase, thereby preventing N-linked carbohydrate addition. Because of the inhibition, the ER in proteins is not properly folded and causes improper proteins to accumulate, activating the unfolded protein response (UPR). Overloading of protein folding stress makes the liver cells attempt to restore balance by inducing chaperones and protein-folding enzymes. If the stress is not mitigated, hepatocytes will necrotize or die. Intraperitoneal tunicamycin injection is typically administered at equivalent doses of 1–5 mg/kg. Hepatocellular apoptosis, oxidative damage, and liver dysfunction are all seen in rats, as in mice. Rats are utilized in more detailed analyses of liver function and biochemical studies, and also in evaluating therapeutic interventions against ER stress, such as the application of inflammatory inhibitors or antioxidants[31].

Lead induced hepatotoxicity

Numerous metals are crucial for gene regulation, cellular signaling, and enzyme function. Naturally present within the lithosphere, lead is a blue-gray, lithally toxic bivalent metal distributed in the environment by a number of human activities. Lipid peroxidation(LPO) and disruption of the redox balance due to production of oxygen based reactive molecules are the main mechanisms responsible for liver injury caused by lead[32]. There are two general mechanisms by which lead toxicity exerts damage by free radicals: (1) formation of reactive molecular oxygen, comprising dihydrogen dioxide, excited-state oxygen, and dihydrogen dioxide, and (2) instant use of antioxidant pools. The initial site of heavy metal-induced oxidative damage is the cell membrane. This is largely due to the alterations of double-bond-containing polyunsaturated fatty acids, which are primarily present in phospholipids of membranes. Lipid oxidation acts as a cytotoxic process conducted by reactive species, and lead is reported to induce oxidative injury through enhanced peroxidation of membrane lipids. The sequence of reactions including commencement, continuation, and resolution reactions leads to LPO. A further significant mechanism of lead poisoning is GSH depletion. GSH is a tripeptide reductive in power and containing a reactive -SH group with cysteine. Through direct interaction with ROS via the -SH group, it functions as a small molecule antioxidant. Otherwise, it can act as a cofactor in the catalutic detoxification process of reactive oxygen species. Lead attaches specifically to the sulhydral group only, reducing the level of GSH and possibly interfering with GSH's antioxidant activity [33]. Rat hepatotoxicity was seen when a one time administration (20 mg/kg, through i.p. injection) acetate of lead was administered to rats, reflected by significant rises in serum values of bilirubin, cholesterol, triglycerides, serum glutamate-pyuruvate transaminase (SGPT), glutamate-oxaloacetate transaminase (GOT), lactic acid dehydrogenease, and acid phosphatase (ACP) [34].

LPS-induced hepatotoxocity

LPS-evoked hepatotoxicity is a most important animal model for studying immune response and inflammation-related hepatic damage. LPS is an component of the permeable membrane of Gram-negative microbes. Lipopolysaccharide antigen stimulate the discharge of inflammatory signailing molecules such as tumor necrosis factor alpha, IL-1β, and IL-6 through TLR4 binding on Kupffer cells, hepatocytes, and endothelial cells of the liver. This cascade of inflammation initiates the generation of ROS and nitric oxide (NO), which induces hepatocellular injury and adds to oxidative stress and cell death. Under severe conditions, the model can lead to acute liver failure or chronic hepatic injury by virtue of a possible failure in the hepatic ability to regenerate. Mice are the most frequently employed preclinical model for LPS-induced hepatotoxicity. Most studies administer LPS intraperitoneally (IP) or intravenously (IV) between 0.5 and 10 mg/kg depending on the goals of the study. Liver cell death, degeneration, and inflammatory cell accumulation are histological markers of this model, as well as augmented liver enzymes (such as ALT and AST) in serum, hepatic inflammation, and oxidative stress in mice. Genetic factors, cytokine profiling, and signal transduction pathways (such as NF-κB activation) triggered by LPS are particularly useful to study with mice.[35]

Cadmium- induced hepatotoxicity

The liver is one of almost all organs in the body affected by cadmium metals and metalloids. Cadmium is one of such metals, and its increasing occurrence as an environmental contaminant is of concern [36]. The liver sustains damage from long-term exposure to cadmium metal. The liver is one of the tissues that are damaged by a high bolus dose of cadmium [37]. By upgrading the peroxide-induced oxidation of cell membrane lipids in tissues and altering the antioxidant cell systems, cadmium induces oxidative damage to a wide range of organs. Since metal ions act on cell organelles, peroxidative destruction to the plasma membrane can lead to damage in other cell constituents [38]. Excessive generation of reactive oxugen species, like dihydregen dioxide, OH ions, and oxygen free radicals, occurs due to cadmium poisoning. The end result of these ROS is increased lipid oxidative damage, congestion in the liver, restricted blood flow, and oxygen deficiency[39]. The ensuing ischemia oxygen deficiency results in inflammation, activation of KCs, and neutrophil invasion, all of which could be contributing factors in the extensive hepatocellular necrosis and apoptosis[40]. Whereas concentrations of blood protein and tissue protein fall, cadmium increases serum levels of carbamide, creatinine, blood sugar, aspartate transainase, acid phosphatase, ALP, ALT, AST, and total bilirubin. Rats were shown to have elevated acid phosphatase when a dose of cadmium (1 mg per kg orally) was administered for 15 days [41].

Sodium arsenite-induced hepatotoxicity

One of the most frequently used animal model for studies on arsenic toxicity and liver effects is sodium arsenite-induced hepatotoxicity. One of the most commonly known inorganic arsenic molecules causing oxidative stress, inflammation, and cell death in liver cells is sodium arsenite (Na_3AsO_3). Arsenic exposure is an important paradigm to study environmental toxin-induced hepatotoxicity since it has been implicated with liver injury, fibrosis, and even liver cancer. Oxidative stress occurs due to metabolism of sodium arsenite by the body to yield excess toxic molecules that generate reactive oxygen species (ROS). All these lead to hepatocyte apoptosis, fatty liver, and destruction of liver cells. Sodium arsenite also disrupts many biochemical processes

within liver cells, including glutathione (GSH) metabolism, cellular signaling pathways, and mitochondrial functions, all contributing to hepatocellular injury. Rats are administered sodium arsenite intraperitoneally (IP), orally by gavage, or in drinking water at doses of 1-5 mg/kg depending on the study design. The liver damage induced by arsenite can be quantified by liver enzyme activities in the serum (e.g., ALT and AST), which are elevated upon hepatic damage. Histological assessment of the liver tissue detects fibrosis, inflammation, fatty degeneration, and hepatocellular necrosis [42].

Aflatoxin B1 (AFB1) induced liver damage

Aflatoxin B1 is a fungal metabolite that occurs naturally and can cause liver cancer in animals and humans and acute hepatotoxicity. In the laboratory and in rats hepatic tissue, AFB1 induces hepatotoxicity by adding to DNA [43]. Through oxidation reactions in the liver, these conjugates are generated by extremely reactive external epoxide products of aflatoxin B1 [44]. This activation has been associated with several cytochromes P450 such as human cytochrome P450 1A2 and cytocrome P450 3A4 [45]. Originally, toxic reaction was assigned to be brought about predominantly by the epoxide's genotoxicity, which depends on the creation of genotoxic modificaton, which at elevated doses are lethal to cells. But it was speculated that the acute toxicity resulted from a aldehyde compoundof Aflatoxin B1 that quickly arises from the epoxide and can adduct proteins [46]. In addition, AFB1 dialdehyde-induced cell necrotic injury can lead to compensatory liver hyperplasia, which can encourage the integration of variation into proliferating cells deoxyribonucleic acid and assist to the tumorigenicity that the aflatoxin B1 reactive metabolite triggers [47]. AFB1 reduces the serum cholesterol level and increases values of bilirubin, alkaline phosphatase, SGOT, and SGPT. Bleeding, necrosis, and intense accumulation of lipids are visible tissue damage and histologic alterration most noticeable in hepatic tissue. Single oral administration of a single dose of aflatoxin (1 mg/kg) in rats induced intensive liver lesions from increased values of serum levels of SGOT, SGPT, and ACP [48].

Chlorpromazine-induced hepatotoxicity

A well-characterized animal model for investigating liver damage caused by the drugs particularly that due to the administration of antipsychotic drugs, is chlorpromazine-induced hepatotoxicity. Toxicities in the liver induced by high doses of the typical antipsychotic drug chlorpromazine (CPZ) can be through various mechanisms, such as oxidative stress, hepatocellular apoptosis, mitochondrial dysfunction, and cholestasisIn realizing the reasons of drug-induced hepatotoxicity, assessing potential hepatoprotectants, and studying the activity of liver transporters and enzymes in drug biotransformation, this model can be applied. Typically, drinking water, intraperitoneal, or oral gavage are used to administer chlorpromazine. Depending upon the experimental format, commonly applied doses range between 10-50 mg/kg/day. Chlorpromazine's liver toxicity in rats can be determined by: Measuring serum concentrations of hepatic enzymes like ALT and AST. Histological examination to seek fatty infiltration, inflammation, necrosis, and hepatocellular damage in the liver tissue.[49]

Halothane-induced hepatotoxicity

Chemically, halothane is 2 bromo 2 chloro 1 trifluoroethane. It has often been used in animal models as an inhalation anesthetic and as a hepatotoxin [50]. It is widely known that CYP450 2E1 system monooxygenases convert the fat

soluable toxin halothane to hepatotoxic metabolites in the liver [51]. Hepatocyte necrosis, degeneration of lipoprotein interrelations in erythrocyte lipid bilayer of human subjects, suppression of membrane enzymic activity, and alteration in the activity of the glucose 6-phosphate dehydrogenase in the brain are thus consequences of halothane anesthesia[52]. Widespread denaturation and centrilobular necrosis are displayed by rat liver when treated with halothane.Hepatotoxicity was shown in both the male and the female rats within 12 hours following administration of an amount of halothane (30 mmol/kg, i.p. route) that was suspended in 2 milliliters olive oil [53].

CONCLUSION

Hepatotoxicity refers to damage to the liver due to chemicals. There are many chemical substances called hepatotoxins, and they are the ones which cause hepatotoxicity. By generating free radicals, these cause injury to liver cells and bring about hepatotoxicity, which causes a range of liver diseases. The article explains how various chemical substances that injure the liver and cause corresponding liver diseases function.

REFERENCES

1. Olsson R, et al. Drug-induced liver injury: 900 drugs and counting. Ann Hepatol 2005;4(4):225-229.
2. Berthelot P, et al. Liver metabolism and its implications in disease. J Hepatol 2021;74(4):841-853.
3. Jaeschke H, et al. Mechanisms of liver injury and protection. Toxicol Pathol 2012;40(7):1012-1027.
4. Mitchell JR, et al. Acetaminophen-induced hepatotoxicity: the role of reactive metabolites. Clin Pharmacol Ther 1973;14(5):717-727.
5. O'Grady JG, et al. NSAIDs and hepatotoxicity. Gut 2001;48(2):213-218.
6. Sarris AH, et al. Hepatotoxicity of methotrexate in rheumatoid arthritis: a review. Semin Arthritis Rheum 2001;30(3):192-202.
7. Kumar R, et al. Isoniazid-induced hepatotoxicity in patients with tuberculosis: a review. Liver Int 2012;32(6):932-939.
8. Bruckert E, et al. Hepatotoxicity of statins: a review of the literature. Am J Cardiovasc Drugs 2005;5(6):279-287.
9. Glauser TA, et al. Hepatotoxicity associated with antiepileptic drug use in children. Epilepsia 2006;47(4):577-580.
10. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. Heavy metal content of ayurvedic herbal medicine products. Jama. 2004 Dec 15;292(23):2868-73.
11. Jaeschke H, et al. Animal models of drug-induced liver injury: current limitations and future perspectives. Toxicol Sci 2012;125(1):239-249.
12. Jaramillo M, et al. Mechanisms of drug-induced hepatotoxicity: role of oxidative stress and inflammation. Redox Biol 2018;15:118-123.
13. Shah VH, et al. Preclinical animal models for drug-induced liver injury: applications in safety testing and mechanistic understanding. J Hepatol 2016;65(1):175-186.
14. Dambach DM, Andrews BA, Moulin F. New technologies and screening strategies for hepatotoxicity: use of in vitro models. Toxicological Pathology. 2005 Jan;33(1):17-26.
15. Hajovsky H, Hu G, Koen Y, Sarma D, Cui W, Moore DS, Staudinger JL, Hanzlik RP. Metabolism and toxicity of thioacetamide and thioacetamide S-oxide in rat hepatocytes. Chemical research in toxicology. 2012 Sep 17;25(9):1955-63.

16. Amin ZA, Bilgen M, Alshawsh MA, Ali HM, Hadi AH, Abdulla MA. Protective role of Phyllanthus niruri extract against thioacetamide induced liver cirrhosis in rat model. Evidence-Based Complementary and Alternative Medicine. 2012;2012:241583.
17. Lee WM. Acetaminophen (paracetamol) hepatotoxicity: a comprehensive update. Hepatology 2008;47(5):1403-1417.
18. Ramachandran A, Jaeschke H. Acetaminophen hepatotoxicity. In Seminars in Liver Disease 2019;39(2):221-234.
19. Handa SS, Sharma A. Hepatoprotective activity of andrographolide from Andrographis paniculata against carbontetrachloride. The Indian journal of medical research. 1990 Aug 1;92:276-83.
20. Kapur V, Pillai KK, Hussain SZ, Balani DK. Hepatoprotective activity of Jigrine on liver damage caused by alcohol-carbon tetrachloride and paracetamol in rats. Indian J Pharmacol 1994;26:35-40.
21. Jaeschke H, Williams CD. Animal models of paracetamol (acetaminophen) hepatotoxicity. Methods Mol Biol 2011;691:255-272.
22. Eliwa HA, El-Denshary ES, Nada SA, Elyamany MF, Omara EA, Asaaf N. Evaluation of the therapeutic effect of whey proteins on the hepatotoxicity induced by paracetamol and alcohol co-administration in rats. IJPRBS 2014;3(2):295-314.
23. Sandhir R, Gill KD. Hepatoprotective effects of Liv-52 on ethanol induced liver damage in rats. Indian J Exp Biol 1999;37(8):762-6.
24. Kono H, Rusyn I. Galactosamine-induced liver injury: mechanisms and therapeutic approaches. Exp Toxicol Pathol 2010;62(3):255-265.
25. Liu Y, Liu J. Mechanisms of carbon tetrachloride-induced hepatotoxicity and protection by natural products. Environ Toxicol Pharmacol 2010;30(2):101-109.
26. Zeashan H, Amresh G, Singh S, Rao CV. Hepatoprotective activity of Amaranthus spinosus in experimental animals. Food and Chemical Toxicology. 2008 Nov 1;46(11):3417-21.
27. Velmurugan V, Arunachalam G. Hepatoprotective activity of methanol extract of stem bark of Prosopis cineraria Linn against carbon tetrachloride induced hepatotoxicity. Int J Pharm Sci. 2014;6 Suppl 2:491-3.
28. Hemieda FA, Abdel-Hady el-SK, Elnga MA. Biochemical and histological studies on H2-receptor antagonist ranitidine-induced hepatotoxicity in rats. Indian J Exp Biol 2005;43(9):782-5.
29. Maddox JF, Luyendyk JP, Cosma GN, Breau AP, Bible RH Jr, Harrigan GG, et al. Metabonomic evaluation of idiosyncrasy-like liver injury in rats cotreated with ranitidine and lipopolysaccharide. Toxicol Appl Pharmacol 2006;212(1):35-44.
30. Gulcin I, et al. The effects of monosodium glutamate (MSG) on liver injury in rats. J Food Sci 2010;75(7):T128-T132.
31. Lemaire M, et al. Tunicamycin induces hepatic endoplasmic reticulum stress and cell death in vivo. J Hepatol 2009;51(1):147-157.
32. Gurer H, Ercal N. Can antioxidants be beneficial in the treatment of lead poisoning? Free Radic Biol Med 2000;29(9):927-945.
33. Gurer H, Ozgunes H, Neal R, Spitz DR, Ercal N. Antioxidant effects of N-acetylcysteine and succimer in red blood cells from lead-exposed rats. Toxicology 1998;128(2-3):181-189.
34. Suganthi V, Gowri S, Gurusamy K. Hepatoprotective activity of Cayratia carnosa on liver damage caused by lead acetate in rats. Sch Res Lib 2013;3(2):76-9.
35. Du X, et al. The role of lipopolysaccharide in liver injury. J Hepatol 2000;33(4):598-606.
36. Jarup L, Berglund M, Elinder CG, Nordberg G, Vahter M. Health effects of cadmium

exposure - a review of the literature and a risk estimate. Scand J Work Environ Health 1998;24 Suppl 1:1-51.
37. Dudley RE, Svoboda DJ, Klaassen C. Acute exposure to cadmium causes severe liver injury in rats. Toxicol Appl Pharmacol 1982;65(2):302-13.
38. Sarkar S, Yadav P, Trivedi R, Bansal AK, Bhatnagar D. Cadmium induced lipid peroxidation and the status of the antioxidant system in rat tissues. J Trace Elem Med Biol 1995;9(3):144-9.
39. Stohs SJ, Bagchi D, Hassoun E, Bagchi M. Oxidative mechanisms in the toxicity of chromium and cadmium ions. J Environ Pathol Toxicol Oncol 2000;19(3):201-13.
40. Rikans LE, Yamano T. Mechanisms of cadmium-mediated acute hepatotoxicity. J Biochem Mol Toxicol 2000;14(2):110-7.
41. Singh N, Rani P, Gupta M, Goel N, Tandan N. Effects of aqueous extract of camellia sinensis on liver markers of cadmium treated rats. E3 J Biotechnol Pharm Res 2013;4(5):89-93.
42. Bermudez E, et al. Sodium arsenite induces hepatotoxicity and oxidative stress in rats. Environ Toxicol Pharmacol 2008;25(1):83-91.
43. Essigmann JM, Croy RG, Nadzan AM, Busby WF Jr, Reinhold VN, Buchi G, et al. Structural identification of the major DNA adduct formed by aflatoxin B1 in vitro. Proc Natl Acad Sci USA 1977;74(5):1870-1874.
44. Swenson DH, Miller EC, Miller JA. Aflatoxin B1-2,3-oxide: Evidence for its formation in rat liver in vivo and by human liver microsomes in vitro. Biochem Biophys Res Commun 1974;60(3):1036-43.
45. Gallagher EP, Wienkers LC, Stapleton PL, Kunze KL, Eaton DL. Role of human microsomal and human complementary DNA expressed cytochromes P4501A2 and P4503A4 in the bioactivation of aflatoxin B1. Cancer Res 1994;54(1):101-8.
46. Neal GE, Judah DJ, Stirpe F, Patterson DS. The formation of 2,3-dihydroxy-2,3-dihydro-aflatoxin B1 by the metabolism of aflatoxin B1 by liver microsomes isolated from certain avian and mammalian species and the possible role of this metabolite in the acute toxicity of aflatoxin B1. Toxicol Appl Pharmacol 1981;58(3):431-7.
47. Roebuck BD. Hyperplasia, partial hepatectomy, and the carcinogenicity of aflatoxin B1. J Cell Biochem 2004;91(2):243-9.
48. Sharmila Banu G, Kumar G, Murugesan AG. Effect of ethanolic leaf extract of Trianthema portulacastrum L. On aflatoxin induced hepatic damage in rats. Indian J Clin Biochem 2009;24(4):414-8.
49. Gauthier ML, et al. Chlorpromazine-induced liver injury in rats: biochemical and histopathological study. J Toxicol Environ Health 2014;77(3):105-114.
50. McLain GE, Sipes IG, Brown BR Jr. An animal model of halothane hepatotoxicity: Roles of enzyme induction and hypoxia. Anesthesiology 1979;51(4):321-6.
51. Spracklin DK, Hankins DC, Fisher JM, Thummel KE, Kharasch ED. Cytochrome P450 2E1 is the principal catalyst of human oxidative halothane metabolism in vitro. J Pharmacol Exp Ther 1997;281(1):400-11.
52. Trulson ME, Ulissey MJ. Halothane anesthesia alters cerebral enzymes: A histochemical study in the rat. Acta Anat (Basel) 1987;130(2):163-7.
53. You Q, Cheng L, Reilly TP, Wegmann D, Ju C. Role of neutrophils in a mouse model of halothane-induced liver injury. Hepatology 2006;44(6):1421-31.

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