HEPATOTOXICITY – ETIOLOGY, EPIDEMIOLOGY, AND MECHANISMS INVOLVED: A REVIEW

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ABSTRACT

The liver is the largest gland of the human body which takes control of both growths as well as regeneration in humans and animals. It is one of the important body organs to maintain homeostasis. One of the biggest reasons for hepatotoxicity isdrug-induced liver injury. The yearly incidence of this is between 10-15per 10000-100000 of the population. The tendency of any substance like any drug or alcohol, any microorganism, or any kind of injury that can lead to any negative or deleterious effect on the liver is known as hepatotoxicity. Hepatotoxicity can be different types including disruption of liver cells and organelles like mitochondria disruption of transport protein, T-cell activation, and hepatocyte apoptosis. Different kinds of hepatic damage can occur due to different kinds of physiological abnormalities including hepatocyte disruption, transport protein disruption, apoptosis of liver cells, and mitochondrial disruption. Chemical induced hepatic damage can also occur these are intrinsic drug reactions and extrinsic drug reactions. Risk factors that can lead to hepatic damage are idiosyncrasy, age, sex, alcohol consumption, and excessive smoking.

Keywords: Hepatotoxicity, Liver, DILI, Liver Injury

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INTRODUCTION:

Hepatotoxicity can occur due to the use of different drugs or risk factors like alcohol consumption and also due to food or dietary supplements. Mainly drugs like Anti-tubercular Drugs, Paracetamol, LAs and Anti-Carcinogens, and many other drugs can lead to hepatotoxicity.[1]There are different types of hepatic damages that occur due to different physiological abnormalities that are hepatocytes disruption, transport protein disruption, and activation of T-cells, apoptosis of liver cells, mitochondrial disruption and injury to the bile duct. Chemical-induced hepatic damage can also occur like intrinsic and extrinsic drug reactions.[2]Liver toxicity occurs in different types which can lead due to different kinds of physiological and chemical abnormalities like hepatocytes disruption, transport protein disruption, apoptosis of liver cells, and mitochondrial disruption**.** All of these factors can lead to liver toxicity and can be responsible for a lot of major and minor diseases and disorders. One of the biggest reasons for hepatotoxicity is drug-induced liver injury (DILI) which can lead to a wide spectrum of different symptoms that range from mild and non-specific symptoms including acute and chronic hepatitis, cholestasis, and transaminitis to failure of the liver.[2]These can be caused multitude of drugs, dietary and herbal supplements lead to withdrawal of drugs from the market. This activity can cause hepatotoxicity, the pathophysiology of management of the patients.[2]

As we eat food, carbohydrates get cleaved into mono, poly, and di-saccharides by different enzymes. The liver is the site of glycogen storage which gets released into the bloodstream to maintain the balance of all metabolic processes.[3]Lipids weigh about 5% of the liver but if it exceeds up to 40-50% it can lead to liver disorders. In the case of lipid metabolism liver play two major roles that are fatty acid synthesis, fatty acids conversions into triacylglycerol, and VLDL.[4]Liver plays a primary role in protein metabolism and also to maintain normal plasma concentration of amino acid. Hepatocytes also known as liver cells have both adaptive and proliferative activity under different metabolic conditions which are promoted by decreasing and increasing the volume of hepatocytes. Under normal conditions, proliferation can hardly occur. Hepatotoxicity is also known as liver toxicity.[5] There are different kinds of systems in our body to maintain homeostasis. The liver is one of the major parts of our body's digestive system. So, if hepatotoxicity will occur the liver will not be able to detoxify the toxin which can lead to an imbalance of the body's homeostasis.[5]

EPIDEMIOLOGY

Drug-Induced Hepatotoxicity has a worldwide yearly incidence between 1.3-19.1 per 1000K individuals exposed and 30% of cases were found to develop jaundice. The prevalence and DILI cause varies geographically. DILI is approximately 10% of all acute hepatitis.[6]This hepatitis is the main cause of short-term jaundice among 50% of patients who present with new cases of jaundice and for up to 50% of the cases of hepatic failure in Western countries.

ALF through DILI is a concern for both patients and clinicians. The ALF of all forms of hepatic failure describes that the cases of idiosyncratic DILI were seen in 10-11 yearsperiod.[7] Data was collected with the help of thorough CRFs from around 1198 topics registered at twenty-three sites in the U.S. which had transplant facilities. Around 11.1%of ALF subjects were found to be considered by professional estimation to have DILI 81.1% were high, 15.0% possible, and 3.8% potential.[8]The subjects were mostly females and there was an over-representation of subgroups for uncertain motives. Around 60 individual causes were concerned; most of them were anti-microbials. Transplant-free survival was around 27.1% but with extremely fruitful transplantation in 42.1%. General endurance was found to be 66.2%. Transplant-free endurance in DILI-ALF was determined by the range of dysfunction of the liver, mainly standard levels of prothrombin, and bilirubin, and the model for end-stage liver toxicity.[7]

The annual incidence of DILI is between 10-15per 10K-100K of the population. A study from France it has been reported a yearly incidence of 13.9 ± 2.4 per 100K population and this was 16X greater than that noted by Regulatory Authorities of French.[9] Such kind of incidence of Hepatic ADRs remains unknown in general and is often underestimated.[10] There are around more than thousands of drugs associated with DILI, mostly Anti-Microbial drugs and CNS drugs. It was reported that women were more prone to develop DILI. In every 10 cases of elevation in ALT in the clinical trials, there can be at least one case of severe DILI that can develop once the drug will be widely available. Hepatic diseases have become complicated and serious worldwide. Every year about 20K to 2.50K cases are reported. The percentage of hepatotoxicity due to different reasons is much higher in developing countries as compared to advanced countries and unfortunately, India is one of them (8-30%).[10, 11.]

HEPATOTOXICITY

The tendency of any substance like any drug or alcohol, any microorganism, or any kind of injury that can lead to any negative or deleterious effect on the liver is known as hepatotoxicity.[6] Hepatotoxicity can be different types including disruption of liver cells and organelles like mitochondria disruption of transport protein, T-cell activation, and hepatocyte apoptosis. Any kind of injury to the bile duct can also lead to hepatotoxicity. Hepatic diseases are now one of the most serious complicated and serious diseases and have become a major cause of both morbidities as well as mortality worldwide.[9]Every year about 20K to 2.50K cases are being reported. The percentage of hepatotoxicity due to different reasons is much higher in developing countries as compared to advanced countries and unfortunately, India is one of them (8-30%).[12] These different reasons include oxidative stress, and different toxins like chemicals, viruses, and alcohol. This can also happen by their bio-activation to chemically reactive metabolites. These can be free radicals too which are well known for their scavenging action and these either hurts the immune system directly by interfering with the cells at their bio-molecular levels. Even in this modern era of everything including the medical field and medicines, synthetic liver protection is not available.[13]So, plant-based natural extracts from different herbal or one can say medicinal plants are used due to their safety and effectiveness to treat different disorders as these are rich in secondary metabolites that are bioactive compounds like phenols mainly in the case of liver and these are potent antioxidants and hence good hepatoprotective. In most cases, drug-induced hepatic toxicity may lead to mild-moderate elevation of tests related to the liver but it can cause fatal outcomes only in rare cases.[14] These can cause liver enzyme elevations that are ALT, AST, ALP, GGT, and total bilirubin cause liver damage as shown in fig. 1 . There is no current test that can predict DILI. Patients with allergic manifestations can lead to elevated autoantibodies and eosinophilia. Drug-induced liver injury can be caused by different problems are liver fibrosis, chronic hepatitis, and cirrhosis. Elevation in serum bilirubin, blood coagulation, and depletion in albumin defect signify different liver damages. In the case of Cholestatic drug-induced liver injury can lead to elevation of ALT as compared to ALP and vice versa.[15]

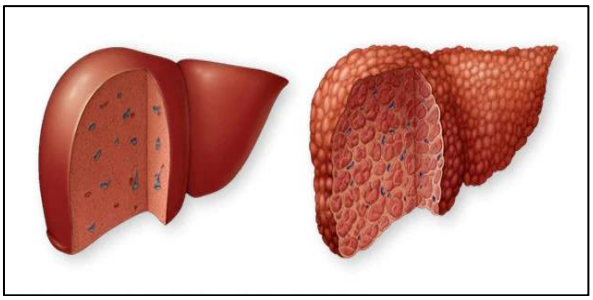

Fig.1 healthy liver vs. apoptotic liver

MECHANISMS INVOLVED IN HEPATOTOXICITY

Different kinds of hepatic damage can occur due to different kinds of physiological abnormalities including Hepatocytes Disruption, Transport Protein Disruption, Apoptosis of Liver Cells, and Mitochondrial Disruption. Chemical induced hepatic damage can also occur these are Intrinsic Drug Reactions and Extrinsic Drug Reactions.[16]

Drugs that can lead to Hepatotoxicity include Liver Necrosis due to drug-like galactosamine, paracetamol can cause Hepatotoxicity, Anti-tubercular Drugs, carbon tetrachloride can cause Liver Fibrosis, Alkyl Alcohol can cause Necrosis, ranitidine can cause Hepatotoxicity and thioacetamide can cause Hepatotoxicity by various mechanisms as shown in Fig. 2.[17]

Dietary Supplements that can cause Hepatotoxicity are Green Tea Extract, Usnic Acid, Vitamin A, Linoleic Acid, ma huang Garcinia Cambogia, Herbal life Products, Hydroxy cut, Lipo Kinetix, Oxy Elite Pro, Anabolic Steroids, and UCP-1. Risk Factors that can lead to hepatic damage are Idiosyncrasy, Age, Sex, Alcohol Consumption, and Excess Smoking.[18]

So, in this review article, we will be focusing on these physiological abnormalities, chemical-induced hepatic damages, risk factors, and dietary supplements that can lead to hepatotoxicity.[18]

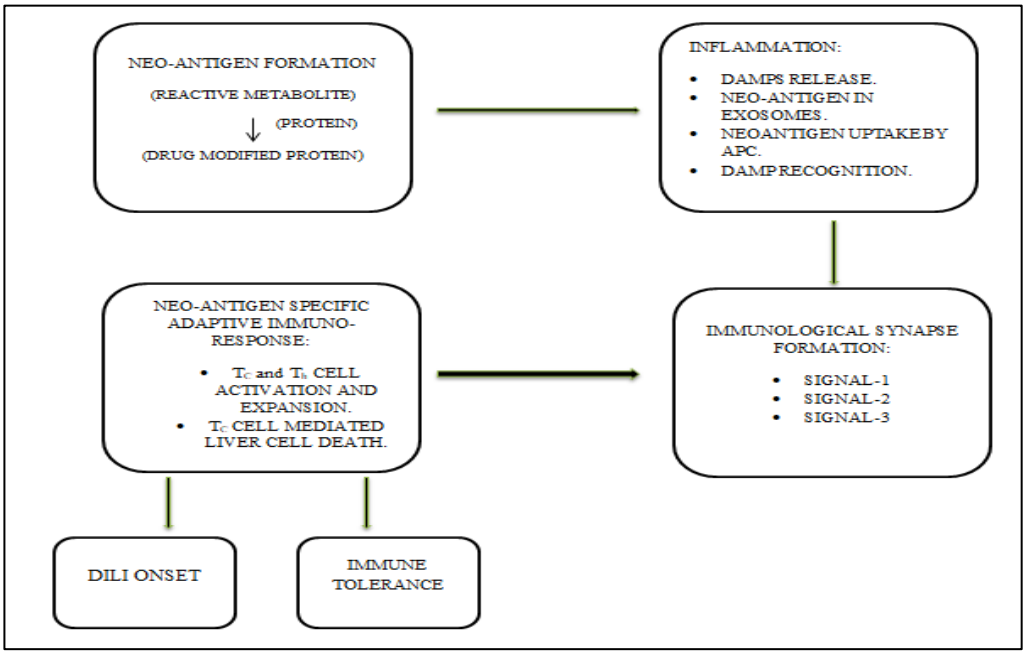

Fig.2 Mechanism Involved In Liver Toxicity.

1. HEPATOCYTE DISRUPTION:

Hepatocytes Disruption can occur by the transmission of death signals to DRs and by an intrinsic pathway that can be stimulated by intra-cellular stimuli. DRs can be activated when the death ligand binds to the DRs. These DRs are present on the plasma membrane of the cells. These ligands belong to the TNF superfamily like Fasl, TNF-α, and TRAIL. DR includes Fas, TRAIL-R and TNF-Receptor. Whenever a ligand binds to the receptor it leads to conformational changes in the binding site that is DR as it induces trimerization.[19] A change recruits in the Cytoplasmic adaptor proteins like FADD hence recruits apoptosis signaling molecules. These all mechanisms collectively form DISC and hence activation of cascade takes place mainly Cap-3, Cap-6, and Cap-7.[20] But, FADD like c-FLIP may cause DISC inhibition and death cell can be prevented.[21] The release of Cytochrome C or other factors space into the cytoplasm from the intermembrane of mitochondria of liver cells can initiate an intrinsic pathway. This release is mediated by a transitional pore. Now in the cytoplasm, a formation of apoptosome leads to activation of Cap-9 which can activate the caspase cascade.[22] This pathway is regulated by Bcl-2 family proteins these are pro-apoptotic and anti-apoptotic. Pro-apoptotic proteins include Bid, Bax, Bak and Anti-apoptotic include Bcl-2 and Bcl-xL. These anti-apoptotic proteins bind to the mitochondria and decrease permeability and inhibit the Cytochrome C release into the cell and gather Bak and Bax.[23] TNF-α when bound to the receptors leads to bidding cleavage in a truncated form and leads to oligomerization of Bax and gets inserted into mitochondria and thus leads to apoptosis. To amplify apoptosis in liver cells, the signals from DRs are not that powerful that they can initiate a cascade but a mitochondrial pathway can be used for this.[24]This amplification plays a major role in apoptosis of liver cells mediated through TNF-α. TNF-α induced apoptosis gets abolished when the intrinsic pathway of apoptosis gets inhibited by Cap-9 blockers. TNF-α can not be able to induce hepatic injury, unlike the Fas ligand. The activation of apoptotic NF- kappa B can be an underlying mechanism. When these NF-kappa get rapidly activated it can induce c-FLIP expression and can weaken the activation on Cap-8.[25]

As the mitochondrial function gets disturbed it can affect other cell organelles to trigger liver cell apoptosis. This apoptosis can occur through the mitochondria-mediated pathway. The signaling of TNF-α and TRAIL involve lysosomal protease released into the cell and hence causes mitochondrial dysfunction.[26]

Liver Cell Apoptosis

As two main pathways-initiated apoptosis, there is one additional pathway too ie. Stress to ER of the cell. Stress to ER of a cell can also cause initiate apoptosis. Factors like Calcium homeostasis alteration, overload, or misfolding of protein can induce stress in ER. The apoptosis can be activated by Bax.[27] Additionally, Oxidative Stress can cause liver cell apoptosis. This can be caused due to overproduction of ROS which is another inducer of Apoptosis. It can harm Mitochondrial DNA (mtDNA), phospholipids, and proteins that can

cause hepatic cell apoptosis.[28]As we know caspase cascade are a very important part of apoptosis of any kind of cell in the body. When apoptosis gets induced without caspase activation or when inhibition of this cascade occurs, this apoptosis can be considered caspase-independent apoptosis. E.g. ROS- induced mitochondrial damage, apoptosis-induced AIF release from mitochondria into cytosol and TNF-α can cause inhibition of caspase cascade. In the case of AIF release, AIF translocation can directly cause condensation of chromatin and cleavage of DNA.[29]Additionally, there is some other modalities of a cell that can lead to cell death and can cause injury to the liver. These can cause highly heterogeneous death processes.[30]Conditions like specific virus infection can lead to the activation of necroptosis that can lead to interaction between RIP1 & RIP3.[31]

2. TRANSPORT PROTEIN DISRUPTION:

Transport Protein Disruption can cause due to two main reasons including the Basolateral Transport System by different mechanisms like Na^+-independent hepatic uptake of amphipathic substrates, Na^+-independent hepatic uptake of hydrophilic organic anions and organic cations, and Basolateral efflux pump.[32] The second cause is Canalicular transport systems which can occur due to different mechanisms including bile salt excretion, Excretion of non-bile salt organic anions**,** Phospholipid excretion, and Copper excretion Shown in Fig. 3.[32]

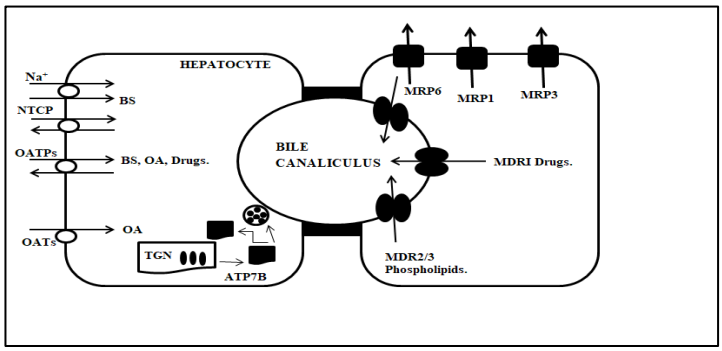

Fig.3 Transport Protein Disruption

BASOLATERAL TRANSPOORT SYSTEM:

Basolateral Transport System can lead to transport protein disruption by different mechanisms including both Na^+ dependent and independent uptake of bile salt of amphipathic substrates.[32]

In the case of Na^+-dependent bile salt uptake in some studies was found that Taurocholate uptake (80%) and Cholate uptake (50%) in the liver cells is Na^+- Dependent.[33, 34] Whereas unconjugated bile salts can traverse the membrane with the help of Passive Diffusion.[35,36]Taurine and Glycine conjugation can cause a decrease in the pKa and the carrier proteins can also be responsible for cellular uptake. Na^+ taurocholate co-transport polypeptide (SLC10A1) is an expression and molecular strategy for the chief uptake system for conjugated bile salts.[44] In the liver, NTCP represents a protein of 349-amino acid.[37] It is structurally related to the IBAT that mediates the Na^+-dependent uptake of bile salts.[38,39]NTCP mRNA and protein levels get decreased in bile duct ligation, endotoxinemia and ethinyl estradiol - induced cholestasis.[40,41] In patients with extra-hepatic biliary atresia and clinical evidence of cholestasis NTCP mRNA levels can also decrease.[42,43,44,45]

The independent uptake of Na^+ cannot be ascribed to a single protein but by a whole family known as OATP-1.[46] This family indicates multi-specific bile transporter.[47] It can help with leukotrieneC_4, hormones like thyroid hormones, BSP, bilirubin, ouabain, ACE inhibitors, HMG-CoA reductase inhibitors, and also oligopeptides.[48]The driving force for OATP mediated transport is not fully known but has been shown that OATP-1 can mediate bi-directional transport of BSP.[49,50]

OATP-2 is 661 amino acid proteins with a molecular mass of 92kD. It has also been detected in the endothelial cells of the retina, BBB, and at the basolateral plasma membrane of the choroid plexus.[51] OATP-2 is homologous to OATP-1, bile salts, cardiac glycosides, digoxin, and ouabain.[52] But the difference is the acinar localization in the liver cells. OATP-1 is distributed within the liver acinus while OATP-2 exhibits a varied lobular distribution in perivenous liver cells but the exception is the innermost one or two layers of the cells surrounding the central vein.[53]OATP-4 can similarly mediate through Na^+-independent uptake of bile salts in hepatocytes and can also represent a whole-body isoform of the so-called "Liver-Specific Transporter-1". OATP-4 helps in the transportation of many organic anions comprising Taurocholate, BSP, steroids, prostaglandins , leukotrienes, T_3, and T_4hormones.[99]

OATP4 is 43% identical to amino acid level with OATP-1 and 44% identical to amino acid with OATP-2. Till date, there are 4 OATPs identified and are called OATP-A, OATP-B, OATP-C, and OATP-8.[54] These are wholly expressed at the basolateral membrane of hepatic cells and show 80% mutual identity. The closest homologue in rat liver is OATP-4.[55]

Additionally, NTCP and OATPs possess a third family called the organic anion transporter family.[56]This family comprises the OAT and OCT and also the OCTN/carnitine transporter families.[57]OAT-2 facilitates sodium-independent transport of α-ketoglutarate and salicylates while-3 transporting PAH, estrone-3-sulfate and the cationic compound cimetidine.[58]

The basolateral membrane also has several members of the multidrug resistance protein family belonging to the ABC-transporter. ABCC1 mediates the ATP-dependent efflux of glutathione S-conjugates, leukotriene C_4, and steroid conjugates. ABCC3 is expressed at the hepatocyte membrane and mediates basolateral efflux of the organic anion's estradiol-17-β-D-glucuronide and S-(2,4-dinitrophenyl) glutathione, anticancer drugs, and even monovalent bile salts.[59] ABCC5 appears to be an anion transporter however its expression level in the adult liver is very low. ABCC6 is localized at the lateral membrane of hepatocytes and transports the cyclic pentapeptide and endothelin antagonist BQ-123. Interestingly, mutations in the MRP6 gene are the cause of pseudoxanthoma elasticum.[60]

Canalicular transport systems

Canalicular excretion signifies the rate-limiting step in the complete secretion of bile salts.[61]Whereas the concentrations of bile salts in the hepatocyte are in the micro-molar range; the concentration of canalicular bile salt is higher, requiring active transport across the canalicular hepatocyte membrane. Depiction of ATP-dependent taurocholate transport in canalicular membrane vesicles specified the occurrence of a particular carrier system in monovalent bile salts.[62]

The BSEP gene locus has been recognized as the positional candidate for advanced intrahepatic cholestasis, an advanced liver disease categorized by low concentrations of biliary bile salt. [63]

The elimination of non-bile salt organic anions into bile can be facilitated by MRP2. MRP2has a molecular mass of 190 kD. The range of organic anions transported by MRP2 is found to be similar to that of MRP1.[64] Numerous dissimilar xenobiotics like glibenclamide, probenecid, rifampicin, indomethacin, vinblastine, and cyclosporine A possess the ability to inhibit the anionic fluorescent dye carboxy-2',7'-dichlorofluorescein (CF) excretion by primary human liver cells suggesting that excretion by the human liver may be compromised by various drugs. MRP2-Mutants can lead to the synthesis of a truncated and non-functional protein.[65]

Phosphatidylcholine (PC) is the chief lipid co-secreted into bile with cholesterol. The continuous replacement of these molecules from the hemi-leaflet of the canalicular membrane is facilitated by the intensive action of ATP-dependent and independent PC.[66]

The liver is the vital organ of Cu-homeostasis with an abundant capacity for the storage and excretion of this metal. The degree of the excretion is directly proportional to the size of the copper pool which indicates that liver cells can nous the copper status in the cytoplasm.[67]Theexcretion of heavy metals like copper is a significant cleansing mechanism of the liver. This mechanism is mediated through a copper transporting ATPase that is ATP7 and expressed mainly in the liver.[68]The molecular mass of this protein kD is localized to the Trans-Golgi network and there it mediates the copper incorporation into cuproenzymes like ceruloplasmin.[69] Copper is most probably taken up into hepatocytes through hCTR1 &hCTR2. As the concentration of copper in the hepatocyte increases, ATP7B reorganizes. Thus, it can induce trafficking of its transporter from the trans-Golgi network to the membrane and can mediate biliary copper excretion.[70]

LIVER CELL INFLAMMATION

Liver cirrhosis, scarring of hepatic cells, or liver failure is a condition of the liver which cannot be undone and occurs due to long-term hepatic inflammation. Liver cirrhosis is a major reason of death in more than 1M worldwide each year. The main cause of this can be a virus-induced infection, alcohol disease, and NASH. Sometimes auto-immune disorders can also be the reason. As different types of reasons can cause hepatic injury, numerous pathways exist to trigger different kinds of immune reactions.[71]So, it becomes really important for us to understand the mechanisms of inflammation and fibrosis to develop different treatments for chronic liver diseases. Hepatic steatosis can cause liver injury in response to ASH, toxins, chemotherapy, and NASH. These injuries can change liver cell gene expression and result in IL-1A, TGF-β, mesenchymal genes, some ligands, and CXCL10. The injured liver cells then lead to inflammation and then fibrosis.[72]

In normal physiological conditions, the liver is exposed to exogenous substances. The capillary system of the liver is lined with Kupffer cells

which are resident macrophages and DCs. As the liver plays a huge role in lipid and glucose metabolism, inflammation in liver cells can lead to different kinds of metabolic disorders like NAFLD.[73]

In this part of the review, the main focus will be on the liver inflammation and crosstalk of myofibroblasts with inflammatory cells as elaborated in Fig. 4.[74]

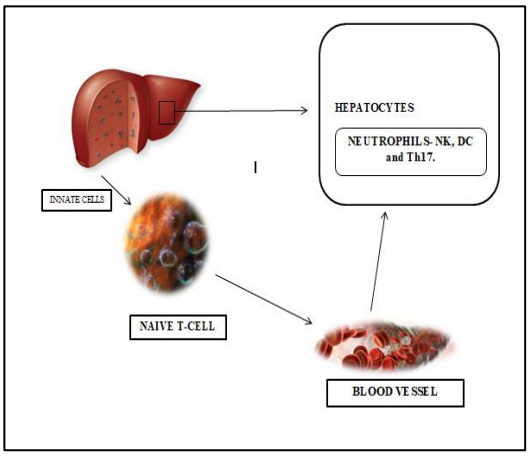

Fig. 4 Liver Cell Inflammation.

LIVER INFLAMMATION: MECHANISM

Liver inflammatory cells play a very important role in the inflammation of the liver. These cells are known as Kupffer cells. These are residence macrophages that are located in the lumen of liver sinusoids. Kupffer cells are about 30% of sinusoidal cells.[75]

In a study, on embryogenesis, it has been found that the macrophages were found to migrate from the yolk sac to fetal liver cells. They were detected as F4/80+ in mice at E-11.[76]Later these proliferate and differentiate into Kupffer cells in the late stage. The macrophage markers are the representative markers of Kupffer cells due to their origin. These markers include CD11b, F4/80, and CD68. It was believed that Kupffer cells are not self-renewable but recent evidence suggests that these can be self-renewing or can derive from local progenitors.[77]

As hepatic cells get injured, Kupffer cells get activated and also express signaling molecules & cytokines. These cells display markers of M1 & M2-like macrophages depending on the signals received. This inflammation can be balanced by pro-inflammatory & anti-inflammatory Kupffer cells. Portal circulation can expose Kupffer cells to different substances like nutrients and bacteria in the gut and remove pathogens and harmful substances via PRP.[78]There are two sensing protein families of PRP that are TLRs and NLRs. Both TLRs and NLRs have their specific functions like TLRs recognize bacterial products derived from gut microbiota.[79]These include LPS and peptidoglycans. These cells give response to LPS by TLR4 and lead to the production of cytokines that are TNF-α, IL-1β, 12, and 18 and in the case of granulomatous liver disease production of chemokines occurs.[80]

The key component of liver inflammation is recruited macrophages derived from bone marrow. There are different types of macrophages including pro-inflammatory, wound healing, and immuno-suppressive phenotypes.[81]

M1-Macrophages, IFN-γ, LPS & TNF-α induce these M1 macrophages. Pro-inflammatory cytokines are expressed by these including TNF-α, IL-6 & 1. In the pathogenesis of hepatic disorders, these are implicated. These are associated with the promotion of glycolysis and NO production by inducible NOS from arginine.[82]

M2 Macrophages, IL-4, 10 & 13 induce these M2 macrophages. These produce IL-10, PDGF, and TGF-β & EGF. Anti-inflammatory effects are produced and wound healing is promoted. These macrophages rely on the oxidation of arginine and fatty acids metabolism by ARG-1.[83]

Both of these also exhibit different metabolic processes. In response to different stimuli, extensive transcriptome analysis for macrophages reveals activation of macrophages between the M1 and M2 poles. Hence, the M1-M2 paradigm can oversimplify liver macrophages exposed to different types of pro-inflammatory and anti-inflammatory stimulation. Bone – marrow-derived macrophages are responsible for tissue re-modeling; these are MMP-9, 12 & IGF-1, and also GPNMB.[84]

HEP-G CELLS PROLIFERATION

CYP2E1 which is Et-OH inducible form which first metabolizes and then activates different important substrates that are toxicologically important that including Et-OH, and CCl4 to different toxic products.[85]This kind of metabolism can lead to oxidative stress by ROS generation that is a possible pathway by Et-OH can turn into a toxin. This induction is a central pathway through which Et-OH can lead to the generation of oxidative stress and in the Intragastric model of Et-OH feeding prominent induction of CYP2E1 leads to alcoholic hepatotoxicity co-link levels of CYP2E1 and elevation in lipid peroxidation can occur which can be further blocked by CYP2E1 blockers.[86] To express human CYP2E1 in cell lines first one needs to understand activity as well as effects. HepG2 cell lines can establish by E9 Cells Method and one more way to do this is by the plasmid transfection method. Both these cells E9 and E47 can express CYP2E1 at about 10-45pmolmg-1 microsomal proteins. Compound that

metabolizes CYO2E1 actively to reactive intermediates like PCM and CCl4 which are toxic to CYP2E1 over expressing HepG2 cells but these cannot control cells which can further validate study models of CYP2E1 induced toxicity.[87]Iron, Et-OH, and fatty acids like arachidonic acid but not others like oleic acid which are considerably more toxic to these than that of MV5 control cells. Toxicity was concentration and time-dependent and is associated with lipid peroxidation.[88] Antioxidants are those substances that possess the ability to inhibit lipid peroxidation and hence can prevent toxicity. The toxicity is related to CYP22E1. This toxicity can be linked to the levels of CYP2E1 and can also increase after transfection with sense CYP2E1 plasmid. This can diminish after transfection with this plasmid. This can lead to cell killing as apoptotic which can be associated with Cap-3 and can be blocked by inhibiting the pan-caspase. Bcl-2 is a proto-oncogene that can block the release of Cytochrome-C during different mitochondrial signaling.[89]This transfection with plasmid can prevent apoptosis. Some factors that can lead to a decrease in the potential of the mitochondrial membrane in overexpressing CYP2E1 are arachidonic acid and iron. This overexpression of cells can also lower ATP levels. HepG cells were also found to be infected with viruses that contain cDNA directed to the powerhouse of the cell by the 27-amino acid of manganese superoxide dismutase.[90,91] These constructs can protect CYP2E1- overexpressing E47 against Fe and arachidonic acid toxicity. GSH is found to be a critical antioxidant. After this depletion of BSO, the Et-OH, iron, and arachidonic toxicity were enhanced. BSO treatment of these cells can cause toxicity even in the absence of added toxicants. These inhibitors and antioxidants can prevent apoptosis and partly necrotic and partly apoptotic. GSH in E47 was increased more than that of C34, E9, and also MV control cells. Increased GSH can lead to an increase in GSH synthesis uses to activate of γ-glutamyl cysteinyl synthase gene and was blocked by antioxidants. Protein and mRNA activity for other enzymes like catalase and microsomal glutathione transferase can also increase in E47 cells. Endotoxin and bacteria trigger the formation of complement factors, TNF-α, IL-1, and CXC chemokines. Each of these aspects can lead to up-regulation of CD11b/CD18 and PMN for ROS development.[92] Additionally; cytokines activation can lead to the expression of adhesion molecules on EC and liver cells. If geared up neutrophils obtain any indication from parenchyma which can further adhere to liver cells and can lead to final activation of neutrophils with deregulation and adherence to oxidative stress that can lead to necrosis of cells. Mediators that have been generated during an injury like LPO and chemokines and becomes signal for further lead to activation and transmigration of neutrophil.[93] Up-regulation of these may reflect a mechanism to detoxify CYP2E-1 derived oxidants. Since CYP2E1 lead to the production of ROS, Et-OH-induced CYP2E1 expression can lead to the promotion of collagen Type-I bio-synthesis by stellate cells. CYP2E1 is typically found in liver cells while these comprise CYP2E1 in very few amounts.[94,95]A co-culture model involving these cells was developed.[96] A time-based elevation in collagen Type I was detected when these cells started to raise. Though, Type-1 when enters the incubation media can coculture. Stimulation of CYP2E1 due to Et-OH seems to be one of the fundamental pathways that can lead to oxidative stress and cause hepatic cell proliferation by affecting various factors as shown in fig 5. .[97,98]

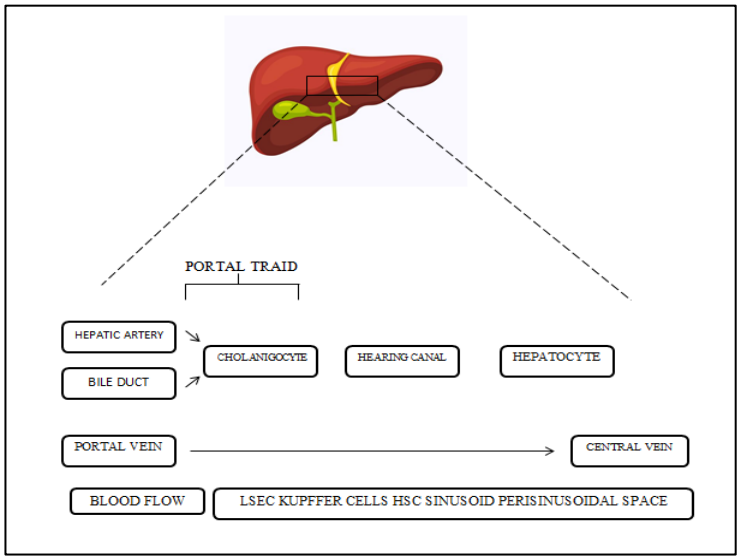

Fig.5. Hep-G Cells Proliferation

1. MITOCHONDRIAL DYSFUNCTION

Mitochondria - a cell organelle a membrane-bound organelle that leads to the generation of most of the energy that is mainly chemical energy. This chemical energy is mostly needed to power the biochemical reactions that are involved in the cells. This energy of mitochondria is stored in the ATP. A MOM and MIM delimit the matrix of mitochondria.[99] 13 polypeptides get encoded by mtDNA of MRC complexes and ATP-synthase, 22 tRNAs, and 2 rRNAs which are needed for intra-mitochondrial translation. Other proteins can be coded by n-DNA which is combined in the cell plasm and exported in the power house of the cell for energy and metabolism. MOM is mediated by mito-fusion while MIM requires Dynamic related protein 1.[100,101] Mitochondrial biogenesis can be regulated by PPARGC1A or by PGC-1a and NRF1. These control mtDNA, and nuclear DNA expressions. The mtUPR maintains the homeostasis of mitochondria and controls the balance of proteins coded by genomes. These ensure proteostasis and mitochondrial quality.[102] Mitochondria are needed for the metabolism of fat and production of energy, urea cycle, iron and amino acid metabolism which regulates pathways that mediate these processes. Mitochondria are responsible for the regulation of innate immune response for inflammation control and different diseases. Alterations of the processes can lead to the development and liver disease progression.[103, 104, 105]

Liver tissues from obese people and NASH have damage to the ultrastructure of mitochondria.[106] MRS is uncoupled and MRS activity of complexes of MRC is decreased causing liver problems of ATP. High levels of ROS and ROS mediated damage in the liver lead to an increase in FFAs increased synthesis, triglycerides, mitochondrial ROS production, high oxidative stress, lipid peroxidation, and decreased ATP levels mentioned below in fig.6 The mechanism for these changes involved mitochondrial ROS alterations and ROS pathways, mitochondrial biogenesis changes, mitophagy, and alterations in cholesterol, GSH, FFA, lipid peroxidation, and TNF.[107]

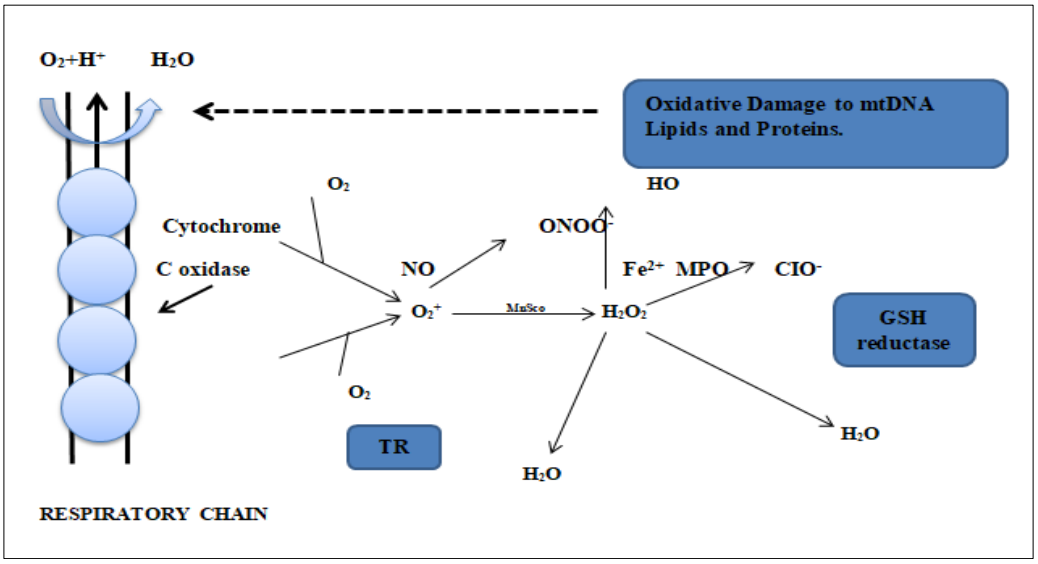

Fig.6 Mitochondrial Dysfunction

CONCLUSION:

Hepatotoxicity is a very common problem with all classes of drugs Most of the cases of DILI reversed after the withdrawal of drug therapy. It is very important to identify and remove the offending agent as quickly as possible to put off the development of chronic liver disease. There are no specific risk factors for DILI, but pre-existing liver disease and genetic susceptibility may bias certain individuals. Although most patients have proven symptoms that are equal to other liver diseases. Treatment of DILI consists of rapid drug discontinuation and supportive care targeted to lessen unwanted symptoms and inhibit apoptosis in liver.

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