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A Mini Review On Liver Injuries Among Humans Due To Drugs And Consumption Of Alcohol

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ABSTRACT:

Liver is the most important vital organ that carries out metabolism of body e.g. formation of cholesterol and triglycerides, synthesis of glycogen, formation of blood clotting proteins and bile formation. Hepatic damage and subsequent liver failure due to both unintentional and intentional acetaminophen overdose has afflicted patients for decades and includes the metabolic cornerstone pathways that exist within hepatocytes in the microsomes. The side effects of drugs on the hepatocytes have been overlooked for years. Drug induced liver injury is the most adverse effect observed in clinical practices. It accounts for around half of acute liver disorder. Anti tuberculosis drugs and acetaminophen overdose are the main issues that result in death from curable diseases. Metabolism of isoniazid and acetaminophen (APAP) results in the formation of toxic metabolites that results in the oxidative stress and glutathione (GSH) store depletion leads to hepatocellular necrosis and steatosis. Alcohol consumption is also the most common cause of liver cirrhosis. Liver peroxidation is considered to be the major mechanism of alcohol-induced hepatotoxicity. To overcome this oxidative stress, there is need of antioxidants that can balance the redox homeostasis of liver by lowering the APAP overdose effect. Consumption of natural antioxidants derived as secondary metabolites from plants in the form of polyphenols and flavonoids prevent oxidative stress. Medicinal plants are best remedies used for hepatotoxicity caused due to oxidative stress. They are cost friendly, easily available and have no mutagenic effect. Herbal medicines form important part of traditional healthcare system of India.

KEYWORDS: Liver, Acetaminophen, Alcohol consumption, Tuberculosis, Oxidative stress

1. INTRODUCTION

Liver is the most important vital organ of our body. The liver performs an impressive variety of essential roles in the body's sustaining, conducting and controlling homeostasis. It involves nearly all the biochemical pathways to development, disease fighting, nutrient supply, energy supply and reproduction. Carbohydrat e, protein and fat metabolism, detoxification, secretion are the main functions of the liver (Pandit et al., 2012). Myofibroblasts are the principal fibrosis effectors

in all tissues. They also contribute significantly to other aspects of the wound healing respons e, including inflammation, angiogenesis, regeneration and normal tissue repair following acute injury and tumor stromal reaction (Lemoinne et al., 2013). To maintain healthy liver in the crucial point for well-being and overall health (Wahlang et al., 2018).. The harmful effects of medications on the liver cells have been overlooked or ignored for a long time at least. Following the establishment of independent drug safety departments in most countries 15-20 years ago, the epidemiology of drug hepatotoxicity remains poorly recorded. The foundations of these organizations were done to evaluate the toxicity of various drugs and to find the alternative methods to overcome their toxicity. Despite all these efforts, the results have been disappointing worldwide. The relative loss has at least three causes. First, it remains difficult to determine drug hepatotoxicity. Second, epidemiological studies are minimal (Larrey et al., 2000).

Hepatotoxicity induced by various drugs:

"Hepatic damage and subsequent liver failure due to both unintentional and intentional acetaminophen overdose has afflicted patients for decades and includes the metabolic cornerstone pathways that exist within hepatocytes in the microsomes. Drug induced liver injury (DILI) is not a common adverse effect observed in clinical practice, since a large variety of substances are metabolized in the liver microsomes including alternative medicines and herbs. The most adverse clinical appearance is fulminant liver failure patients without history of liver disorder present with liver encephalopathy and coagulopathy preceding jaundice Devarbhavi et al., 2010)**.** Drug induced hepatic toxicity is usual cause of damage of the liver. It accounts for around half of acute liver disorders". On >1 occasion, an additional 1000 drugs were involved in causing liver disease (Ramchandran et al., 2018).

Tuberculosis (TB) is one of the main issues that result in death from curable disease. In 2004, there were about 9 million new cases and 1.7 million people died that year from TB. The highest mortality rates are found in Sub-Saharan Africa due to HIV-AIDS, while South-East Asia has the highest number of deaths due to TB. Recommended routine for TB is isoniazid, rifampicin and pyrazinamide regimen for 2 months, followed by isoniazid and rifampicin for 4 months. Ethambutol is typically applied to this protocol and streptomycin recommended by WHO in developing countries for retreatment cases. Hepatotoxicity is the most common side effects of anti-tuberculosis therapy. Drugs used to treat TB induced hepatotoxicity and causes major mortality and morbidity. It also reduces the efficacy of further medications. Anti-tuberculosis drug induced hepatotoxicity (ATDH) results in the elevation of alanine aminotransferase (ALT) five times more than the normal range (Tostmann et al., 2008) Fig 1.

Liver injuries in general population:

Both human and animal case studies indicate that hepatotoxicity induced by isoniazid mainly manifests as hepatocellular necrosis and steatosis and suggests that metabolites of isoniazid covalently bind to cellular macromolecules (Devarbhavi et al., 2010). Mostly anti tuberculosis drugs are lipid soluble and elimination of these drugs need their biotransformation into soluble compounds and is performed through a series of hepatic enzymes (Phase I and Phase II). During Phase I, demethylation or oxidation occurs by cytochrome P450 enzymes. Further compound formed is still not water-soluble and needs more metabolisms. Now reactions of Phase II results in the formation of toxic metabolites which are further converted to non-toxic compounds by glucuronidation and sulfation. These non toxic metabolites are then easily removed. Receptors and transporters contribute significantly in elimination of the drugs. This is sometimes called as III Phase of metabolism

(Kliewer et al., 2002). Previous studies have demonstrated that acetyl hydrazine is highly toxic compound formed due to metabolism of isoniazid that is responsible for drug-induced hepatotoxicity (Raghu and Karthikeyan, 2016).

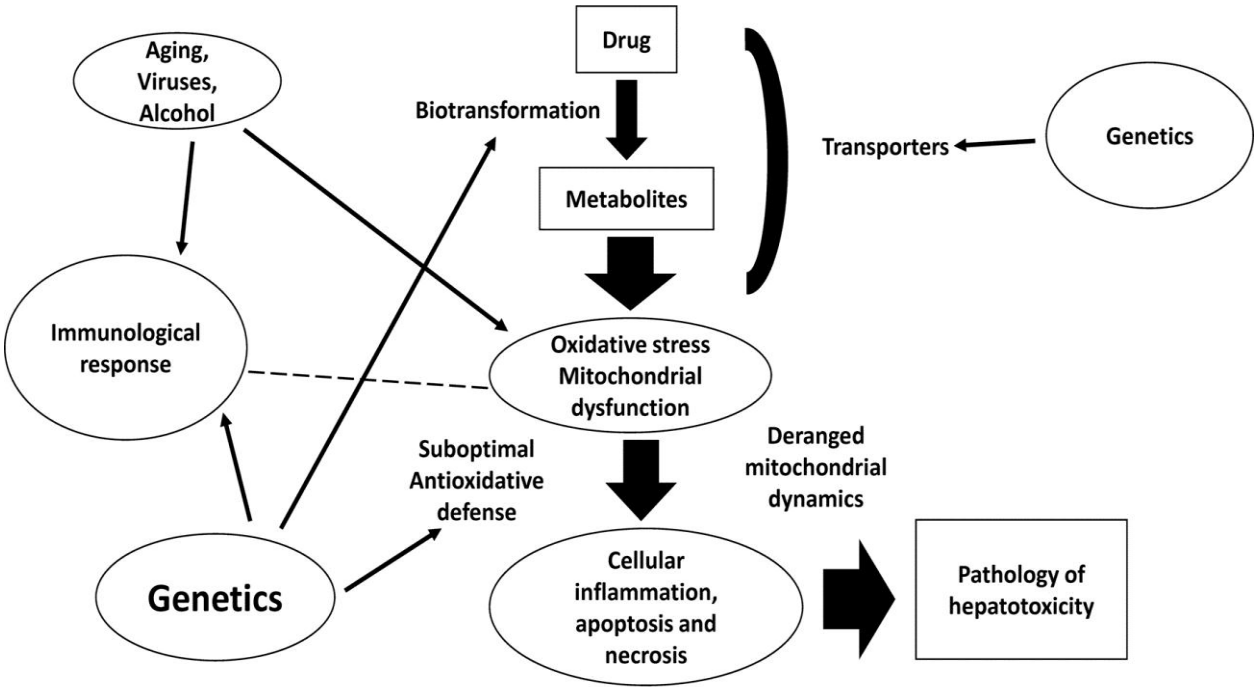

Figure.1 First line anti-tuberculosis drug induced hepatotoxicity (Yew et al., 2018).

Acetaminophen (APAP) commonly known as paracetamol is a drug being used widely due to its antipyretic and analgesic properties (Marcondes-Alves et al., 2019). Its usage is effective and safe at therapeutic dosage but overdose can cause acute liver injury (Lancaster et al., 2015). In general, the prescribed dosage of APAP is 325-650 mg orally after every 4-6 hours regularly with maximum of 4 gm per day. Wherever, the suggested dosage for children is 10-15mg/kg after every 4-6 hours with maximum dose of 50-75mg/kg daily (Schilling et al., 2010). At conventional dosage, 90% of APAP is metabolized to sulfate and glucuronide by sulfotransferase and glucuronyltransferases respectively and is eventually excreted by urination, 2% of APAP remains unchanged and is removed as such in urine. Remaining 5-10% is metabolized to N- acetyl p-benzoquinone imine (NAPQI), a highly reactive metabolite through cytochrome P450 (Sing et al., 2017a, 2017b). Overdose of APAP can lead to saturation in the enzymatic levels of sulfotransferase and glucuronyltransferases, so drug gets diverted to cytochrome P450 and further lead to excessive production of NAPQI in hepatocytes. The elevated levels of NAPQ1 promotes glutathione (GSH) depletion leading to APAP- protein adduct formation in liver cells and finally causes apoptosis or liver necrosis (Singh et al., 2017a) (Fig 1)**.** Some previous documents have revealed that GSH plays a vital role in detoxifying the toxic metabolites or by-products of APAP metabolism (Fig. 2). Metabolism of APAP results in the formation of reactive oxygen species (ROS) or (RNS) and these reactive species possess abilities to bind with biomolecules (Saito et al., 2010). Excessive production of free radicals causes oxidative damage and this result in several pathological conditions including carcinogenesis, aging, stroke and hepatotoxicity (Floyd, 1990). Documented cases of APAP-induced hepatotoxicity first appeared in the mid 1980's in the United States and all signs point to increasing incidence since. It has been confirmed that

this is one of the most popular pharmaceutical products causing DILI. 1-5 mortality rates in opioid patients have been approximated at 0.4%, equivalent to about 300 deaths in the United States per year. In United States, near about 130 million prescriptions were filled for APAP in the year 2010. It is appraised that 63% of unintentional overdoses of APAP happen with the consumption of APAP combination. United States FDA acknowledged the hazards associated with the prescription of APAP combinations and narcotic analgesics and implemented a fixed amount of APAP in various combinations in January 14, 2014 (Yoon et al., 2016).

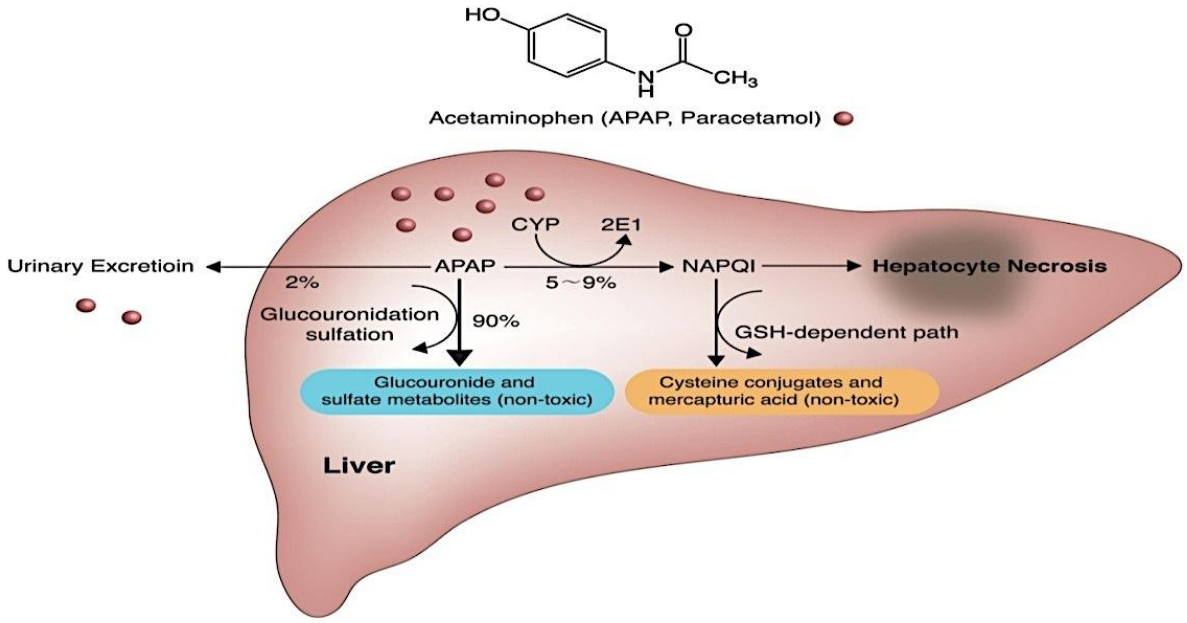

Figure 2: Acetaminophen induced hepatotoxicity in the form of hepatic necrosis (Yoon et al., 2016).

Hepatocytes are having a special defense pathway to fight against oxidative stress, cancer and some neurodegenerative disorders. One of the important antioxidant stress response pathway is Nrf2-antioxidant response element signal pathway (Li et al., 2015). Nrf-2 is a transcription factor binded to a protein known Kelch-like ECH-associating protein 1 (KEAP 1) present in its inactivated form in the cytosol of cells. Uninhibited production of free radicals acts as a stimulus for the activation of Nrf-2 factor by degradation of Nrf2-KEAP 1 protein association by phosphorylation of Nrf2. After dissociation Nrf-2 moves to nucleus to induce the expression of various antioxidant and detoxifying enzymes (Senger et al., 2016). Nrf-2 targeted genes express some antioxidant enzymes such as hemeoxygenase-1 (HO-1) and gamma glycine cysteine ligase (γ-GCL). HO-1 is an enzyme used to break heme into carbon monoxide (CO), iron (Fe) and bilirubin. In mammals, three types of hemeoxygenase are identified such as HO-1, HO-2 and HO-3. In humans HO-1 is present and is made of 288 amino acids. Earlier the metabolites of heme were considered of no use but now they are categorized as internal antioxidants. Bilirubin and biliverdin are regarded as two important antioxidants analyzed both *in vitro* and *in vivo*. Under stress conditions HO-1 translocate to nucleus and regulates it own expression. Various intracellular signaling factors contribute to the HO-1 expressions such as Nrf-2, MAPK, Tram track, AP-1 etc. Acetaminophen overdose induce the expression of HO-1. HO-1 prevents cell death by activation of P38 kinase pathway by increasing the BCL-XL expression (anti-apoptotic protein) and decreases the expression

of apoptotic protein namely Beclin-1 and LC3B-II) (Rasool et al., 2010). Another important antioxidant enzyme γ-GCL is used for the synthesis of GSH. It is a heterodimer made of two subunits modifier (GCLM) and catalytic (GCLC) subunits. GCLC posses all catalytic activities and GCLM has no catalytic activity but enhances the efficacy of GCLC (McConnachie et al., 2007). So Nrf-2 acts as a cellular defense mechanism in case of APAP hepatotoxicity (Cederbaum et al., 2009).

Hepatotoxicity caused due to Alcohol consumption:

"During the metabolic reactions of body, free radicals or reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced in the body in small quantities. These free radicals can damage biomolecules such as proteins, lipids and DNA. Consumption of ethanol can increase the generation of ROS resulting in oxidative stress in many tissues especially liver tissues causing acute and chronic liver disorders (Kay et al., 2011).". The most common single lethal chronic disease caused due to alcohol intake globally is liver cirrhosis. Approximately, 15% of all alcohol consumed deaths resulting from cirrhosis of liver in 2004. It is therefore no surprise that hepatic cirrhosis has always been included in regular lists of alcohol-assigned diseases (Zhang et al., 2019). Meta analysis has showed the positive correlation between alcohol usage and cirrhosis of liver (Zhang et al., 2019). Lipid peroxidation is considered to be the major mechanism in alcohol induced liver toxicity. Earlier studies have suggested several mechanisms to play a key role in how ethanol causes oxidative damage. Aldehydes (reactive product) generates by oxidation of ethanol through aldehyde dehydrogenase and damage mitochondria, which in turn decreases the ATP synthesis. Many studies have investigated that protein carbonyl formation and lipid peroxidation increased by alcohol are the reason of alcohol-induced hepatotoxicity. Alcohol induced hepatotoxicity has been associated with oxidative stress that in turn effects antioxidant defense system of hepatocytes (Kay et al., 2011). Various *in vivo* and *in vitro* studies showed that alcohol causes oxidative stress resulting in hepatocytes damage. It was also demonstrated that metabolism of ethanol through alcohol dehydrogenase results in hepatocytes apoptosis (Wang et al., 2016).. It is investigated that regular alcoholics are at elevated risk of paracetamol-induced hepatotoxicity not only after its overdose but also with its prescribed dosage. Increased sensitivity would be attributed to the activation by ethanol of liver microsomal enzymes with increased production of NAPQI (toxic metabolite) (Coskun et al., 2005).

To counter balance this oxidative stress, there is need of antioxidants that can balance the redox homeostasis (Li et al., 2015).. Consumption of natural antioxidants derived as secondary metabolites from plants in the form of polyphenols and flavonoids prevent oxidative stress. A number of antioxidants like superoxide dismutase (SOD), glutathione peroxidase (GSHPx), vitamin C and E and catalase (CAT) protect cells from serious pathological conditions (Coskun et al. 2005). Drug and alcohol induced hepatotoxicity disturb the redox homeostasis and cellular defense mechanism of liver cells so there is a need of natural antioxidant supplement to reduce the ROS generated liver disease (Olalye et al. 2008). Relieving various diseases using medicinal herbs is as older as mankind. Man is involved in the search for drugs in nature from beginning. There are various evidences from different sources such as preserved specimen and monuments, written documents and even plant medicines originally. Plants are considered to be the gift from nature and are used for the synthesis of various medicinal compounds. Chinese book namely "Pen T Sao" has been written on grasses and roots by shen Nung Circa in 2500BC. In this book, 365 drugs were described being prepared from dried medicinal plants. Some of them are used even nowadays such as camphor, ginseng and cinnamon bark (Petrovska, 2012). Many medicinal plants were

brought into Europe with the journey of Marco Polo in tropical Asia, China and Persia (1254-1324) and Vasco De Gama to India (1498). Various botanical gardens were emerged in Europe and efforts were put forward for the production and cultivation of medicinal plants. Presently, almost every pharmacopoeia all over the world USP XXXI, Eur 6, BP 2007 prescribes medicinal plants of having highest properties rather than using chemical drugs (Petrovska, 2012). Plants consist of majority of heme oxygenase-1 inducers. These plants are used as food, flavouring agents, spices and medicinal herbs (Doberer et al., 2010). Various transcriptional factors of intracellular signaling molecules are in association with HO-1 expressions like MAPK, Tram track, Nrf-2, Broad complex (BTB) and Bric a brac and Bach 1 (Ali et al., 2008). Herbal medicines form important part of traditional healthcare system of India. Holy Bible and some Jewish books also contain some data regarding treatment of various diseases using aromatic plants (Ali et al., 2008). "The consumption of medicinal herbs is found in Upnisheda 1000-600 BC, Ayurveda 1500 BC, and *Rigveda* 1500-400 BC. About 17000 species of herbal plants are found in India. Out of which 7500 are categorized as medicinal plants used to treat various diseases (Kumar et al., 2009). Medicinal plants are best remedies used for hepatotoxicity caused due to oxidative stress. They are cost friendly, easily available and have no mutagenic effect". Medicinal plants have curative effects in many diseases including neurodegenerative diseases and plant derived products moderating Alzeihmer's disease symptoms have been discussed by Anand et al. (2017) in details. It is found that ameliorating effect of chicory fruit extract is observed against 4-tert octyl phenol induced liver injury and oxidative stress (Saggu et al., 2014).

*Conflicts of interest***:** None

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