

Anti-Tuberculosis Drug-Induced Hepatotoxicity: A Review

¹Khushboo Ambreen, ²Rolee Sharma, ³Kaleshwar P. Singh and ^{1*}Sudhir Kumar

¹Human & Molecular Genetics Laboratory, Department of Zoology,
University of Lucknow, Lucknow, India.

²Department of Biotechnology, Integral University, Lucknow, India.

³Department of Microbiology, King George Medical University, Lucknow, India.

*Corresponding Author: E-mail: panwarsk40@gmail.com,

Tel: +91-522-2740074; Fax: +91-522-2740230

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ABSTRACT:

Hepatotoxicity, a serious adverse drug reaction in tuberculosis (TB) patients receiving anti-TB drugs, is one of the most challenging clinical problems worldwide. Despite increasing awareness of clinicians and public, even now it remains an enormous problem and causes of hospitalization and life-threatening events. Considering the importance of anti-TB drug-induced hepatotoxicity (DIH) as a major obstacle to achieve successful treatment of TB, this review article deals with the current understanding of anti-TB-DIH, its incidence, mechanism of liver damage induced by different anti-TB drugs and various risk factors responsible for anti-TB-DIH, which might provide suitable information for future studies to develop safer treatment for TB. Further, this review article focuses on the role of oxidative stress in the pathogenesis of anti-TB-DIH. In addition, the possible involvement of genetic polymorphism of drug metabolizing enzymes with respect to anti-TB-DIH is also discussed in this review.

Key words: Anti tuberculosis drugs, Hepatotoxicity, Mechanism of hepatotoxicity, Risk factors, Oxidative stress, Genetic polymorphism of drug metabolizing enzymes.

[I] INTRODUCTION

Tuberculosis (TB) remains one of the most serious infectious diseases and a major cause of disability and death worldwide, despite noteworthy socioeconomic development and advances in medical sciences [1]. Approximately, one third of the world population is reported to be infected with TB [2]. More than 90% of global TB cases and deaths occur in the developing world [3]. It is a curable disease, however still millions of people suffer every year and a number of them die from

this infectious disease resulting in devastating social and economic impact. In 2012, there were an estimated 8.6 million incident cases of TB and 1.3 million people died from the disease. Also, the burden of disease caused by TB remains enormous in India, causing highest morbidity and mortality rate of any country in the world [1].

Although, anti-TB drugs are available for curing patients with TB, however, many adverse effects attributable to anti-TB therapy poses a

significant hazard both to the physician and the patients in continuing the therapy and further, decreases treatment success rates and may eventually have negative impact on TB control. Among various adverse effects of anti-TB drugs, hepatotoxicity is the most catastrophic consequence, and a vital problem not only to patients, but also to physicians, regulatory agencies and drug developers, which ultimately leads to treatment interruptions, drug resistant development, severe liver injury and even death in TB patients [4].

Therefore, anti-TB drug-induced hepatotoxicity (anti-TB-DIH) is an increasing concern in the treatment of TB. In view of the concern about the risk of hepatotoxicity, in this article we expand our view on the understanding of hepatotoxicity due to anti-TB drugs and report an overview regarding the putative risk factors, which lead to increased risk of DIH.

[II] ANTI-TB-DIH

Hepatotoxicity refers injury or damage to the liver caused by a drug, chemical or other agents. In other words, hepatotoxicity is the ability of chemicals to produce liver injury that leads to diminished liver function. Chemicals that cause liver injury are called hepatotoxins [5].

Hepatotoxicity induced by anti-TB drugs is the most frequent and non-infectious causes of liver toxicity in TB patients, and represents a major challenge for clinicians, the pharmaceutical industry and regulatory agencies worldwide [6]. According to Shakya et al. (2006), anti-TB-DIH encompasses a wide spectrum of liver injury and may be associated with permanent injury and death, if not detected at an early stage [7]. In addition to acute liver failure, DIH are increasing being recognized as causes of cirrhosis, liver cancer and finally death [8]. According to Zaleskis (2005), hepatotoxicity is a serious adverse complication of anti-TB therapy, which is ranging from asymptomatic elevation of serum transaminases to acute liver failure [9]. The first line anti-TB drugs namely Isoniazid (INH), Rifampicin (RIF) and Pyrazinamide (PZA) have been implicated in causing hepatotoxicity [10]. Among these anti-TB drugs,

INH is mainly responsible for the occurrence of anti-TB-DIH [11,12]. INH associated severe liver injury cases have been reported by Wu et al. (2007) [13]. Similarly, significant morbidity and mortality due to INH associated liver injury have been showed in other previous studies [14,15]. However, the combined use of INH and other anti-TB drugs have been associated with an increased risk of hepatotoxicity. Taneja and Kaur (1990) conducted a prospective study of different side effects and toxicity of different anti-TB drugs in 125 cases of pulmonary TB. The incidence of INH associated hepatitis was 6%, where as the incidence of hepatotoxicity with INH plus RIF was 30%, indicating that combination treatment increases the incidence of hepatotoxicity [16]. Purohit et al. (1983) studied the hepatic toxicity due to RIF and found that 7% of patients on RIF containing drug regimen developed transient hepatitis as compared to none (0%) patients on non-RIF drug regimen [17]. In 2003, Yee et al. observed the adverse effects of PZA in terms of hepatotoxicity [18].

[III] INCIDENCE OF ANTI-TB-DIH

The recorded incidence of anti-TB-DIH varies worldwide and has been reported to be higher in developing countries, where factors such as malnutrition, acute or chronic liver disease, indiscriminate use of drugs, and more advanced TB have been concerned [19, 20]. Overall, hepatotoxicity attributed to anti-TB drugs has been reported in 5%-28% of patients treated with anti-TB drugs [21]. In 2002, Huang et al. reported an incidence of 14.7% for anti-TB-DIH in Taiwanese population [22]. In one study that was conducted on Nepalese population the incidence of hepatotoxicity associated with anti-TB drugs was 8% [23]. In Turkey, the incidence of anti-TB-DIH was 8.1% [24]. Similarly, Schaberg et al. (1996) reported an incidence of 11% in the population of Germany [4]. In Indian population, the incidence for anti-TB-DIH was 14.3% [25]. The variation in anti-TB-DIH incidences may be related to differences in patient's characteristics, regimens used, type of monitoring and the diagnostic criteria defining hepatotoxicity [26].

[IV] CLINICAL FEATURES OF ANTI-TB-DIH

Hepatotoxic effects of anti-TB drugs usually occur in the first 2 months of treatment, but may happen at any moment during the treatment period. The symptoms of anti-TB-DIH are jaundice, abdominal pain, nausea, vomiting and anorexia. However, laboratory liver function testing is required to confirm the diagnosis of anti-TB-DIH [27]. Shakya et al. (2006) also showed similar clinical manifestation of anti-TB-DIH in their study [7]. These hepatotoxic effects due to anti-TB-drugs may be relieved by interrupting the treatment at an early stage, because early detection can decrease the severity of hepatotoxicity if the drug is discontinued [28, 29].

[V] MECHANISM OF ANTI-TB-DIH

5.1. Role of liver in the metabolism of anti-TB drugs

Liver is the largest glandular organ of the body, which lies on the right side of the abdominal cavity beneath the diaphragm. It is the most susceptible organ of the body, to toxicity from foreign agents. The majority of drug metabolism process is found to be associated with this metabolically active tissue. Endoplasmic Reticulum, which plays a substantial role in the drug metabolizing activity of liver cells and detoxify harmful drugs and metabolic by-products by converting lipid-soluble exogenous and endogenous compounds into water-soluble metabolites which can be easily excreted by the kidney [30]. Liver has a extensive range of functions including glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production and detoxification. Factors responsible for its contribution include its large size, entero-hepatic circulation (it is perfused by blood containing drugs absorbed from the gut) and rich concentration of most of the drug metabolising enzymes relative to other organs [31].

5.2. Hepatotoxicity induced by INH

Among the first line anti-TB drugs, most cases of anti-TB-DIH have been attributed to INH [32]. Therefore, an understanding of its

metabolism may allow more significant interpretation to reach the key goal of mechanisms underlying hepatotoxicity. N-acetyltransferase 2 (*NAT2*) and cytochrome P4502E1 (*CYP2E1*) are the two main enzymes that play a noteworthy role in the metabolism of INH. In the liver, firstly, INH is metabolised to acetylisoniazid via hepatic enzyme *NAT2* and is followed by hydrolysis to acetylhydrazine. Further, acetylhydrazine is oxidised by *CYP2E1* to form hepatotoxic intermediates, which destroy hepatocytes resulting in liver injury [33]. Glutathione S-transferase (*GST*), an important phase II detoxification enzyme, plays a defensive role against hepatotoxic products that are generated from *CYP2E1*, by conjugating glutathione with toxic metabolites [34]. These conjugated toxic products further eliminate from the body and diminish the toxic effect [35]. The other metabolic route of INH leads to the production of toxic metabolite hydrazine by the process of direct hydrolysis. *NAT2* is also responsible for converting hydrazine to acetylhydrazine and further diacetylhydrazine, a nontoxic component [36, 37]. **[Figure-1]**

Also, INH is a potent inhibitor of several forms of cytochrome P450 including *CYP1A2*, *2A6*, *2C19* and *3A4*. Among these cytochromes, *CYP1A2* play a key role in the detoxification of hydrazine. Therefore, INH is the most likely to cause its own toxicity, possibly by the inhibition of these enzymes [38, 39].

5.3. Hepatotoxicity induced by RIF

RIF is a semisynthetic antibiotic derived from the rifamycins, a group of antibacterials produced by *Streptomyces mediterrane*. In the liver, during the metabolism of RIF, the formation of desacetyl rifampicin takes place by the process of desacetylation [40, 41] and further, a separate pathway of hydrolysis produces 3-formyl rifampicin. The anti-bacterial activity of RIF is mainly attributed with these reactive metabolites. However, the risk of hepatotoxicity is not connected with the activity of these metabolites [42, 43].

Although, RIF can cause hepatotoxicity when taken concurrently with other anti-TB drugs. The occurrence of mortality associated with

hepatotoxicity has been reported to be 16 in 500,000 patients receiving RIF [6]. RIF is an effective inducer of *CYP2E1* isoenzymes and plays a key role to increase INH induced toxicity, most probably by increasing the formation of its toxic metabolite hydrazine, resulting in elevated liver enzyme level and consequently attributed to damage structural integrity of liver [44]. RIF also increases the metabolism of INH to isonicotinic acid, which is also a hepatotoxic product. The plasma half life of acetyl hydrazine (INH metabolite) is shortened by RIF and acetyl hydrazine is quickly converted to its active metabolites by increasing the oxidative elimination rate of acetyl hydrazine, which is related to the higher occurrence of liver necrosis [45, 46]. Therefore, the activity of RIF has been attributed to their ability to increase the incidence of anti-TB-DIH.

5.4. Hepatotoxicity induced by PZA

PZA is only used in combination with other drugs such as INH and RIF in the treatment of TB. PZA is a pyrazinoic acid (PA) prodrug, which is an active inhibitor of *Mycobacterium tuberculosis*. Studies have shown that TB patients treated with PZA, 16% had increased liver enzymes, 7.9% had 5 times more liver enzymes than normal, and 5.3% had hepatitis symptoms [47, 48].

In the liver, firstly, PZA is metabolized to pyrazinoic acid (PA) by the enzyme liver microsomal amidase and further oxidized to 5-hydroxy pyrazinoic acid (5-OH-PA) by xanthine oxidase [49, 50]. [Figure-2]. These two reactive metabolites of PZA are considered to have hepatotoxic potential. The concentration of PZA was found to be decreased in patients with severe hepatotoxicity, probably because of increased conversion to 5-OH-PA and PA, which support the hypothesis that 5-OH-PA and PA are the main toxic metabolites responsible for PZA-induced hepatotoxicity. However, 5-OH-PA is the more toxic metabolite as compared to PA, responsible for PZA-induced hepatotoxicity [51].

5.5. Ethambutol and Streptomycin

Ethambutol (ETH) is also a semisynthetic antibiotic, which is used only in combination

with other agents such as INH and RIF. ETH therapy has been found to be associated with minor, transient and asymptomatic elevations in serum aminotransferase levels. Very rare cases of acute and symptomatic liver injury have been reported in some patients taking ETH [52]. However, the mechanism of liver injury due to ETH is still unclear. No hepatotoxicity has been reported in case of Streptomycin (STR).

[VI] RISK FACTORS FOR ANTI-TB-DIH

Many factors are found to predispose patients towards hepatotoxicity of anti-TB drugs. Detection of these risk factors for hepatotoxicity may play an important role in minimizing the incidence. Also, the identification of high-risk patients would be useful to allow early detection and reduce the morbidity and mortality due to anti-TB-DIH. [Figure-3].

6.1. Age

Patients belonging to younger age group have been found to be at higher risk for anti-TB-DIH [7]. However, several studies suggested that increasing age is a potential risk factor for anti-TB-DIH [53, 54]. One study reported that the rate of anti-TB-DIH ranges from 2 to 8% as age increases, with an average of 5% [55]. Other studies reported that hepatotoxicity ranges from 22 to 33% in patients older than 35 years compared with a range from 8 to 17% in those younger than 35 years [22, 56]. Also, Mahmood et al. (2007) reported that older age group was affected more than the younger age group for anti-TB-DIH (25.8 and 14.4%, respectively) [57]. Marazuki et al. (2008) reported no significant association between age and the risk of developing anti-TB-DIH [58].

6.2. Sex

Anti-TB-DIH was found to be closely associated with female sex [59]. Though, some studies showed no increased risk of anti-TB-DIH in women [60, 33]. Several studies report females at an increased risk of anti-TB-DIH as compared to males [53, 54]. Mahmood et al. (2007) reported a higher incidence of anti-TB-DIH in females than males (26.3% vs. 19.7%) [57]. Female gender was also considered to be one of the potential risk factors contributing to the high

incidence of anti-TB-DIH by Singh et al. (1996) [61]. Difference in DIH incidences between males and females is mainly attributed to slow acetylator status of females, due to which, females are more predisposed to the risk of hepatotoxicity [62].

6.3. Malnutrition

Malnutrition (detected by Body Mass Index $<18.5 \text{ kg/m}^2$) is the leading risk factor globally in terms of the burden of anti-TB-DIH [57, 55]. According to Saukkonen et al. (2006), patients with low BMI had increased incidence of anti-TB-DIH [63]. A study in India showed that the incidence of anti-TB-DIH was found to be three times higher in malnourished patients as compared to healthy controls [20].

6.4. Pre-existing liver disease

Pre-existing liver disease is also a potential risk factor for anti-TB-DIH. An increased risk of hepatotoxicity during TB treatment was observed in patients with pre-existing liver disease (abnormal baseline transaminases) [64, 65]. Hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections are common causes of the chronic liver disease that is frequently seen in populations at risk for TB infection. Several studies show that HBV and HCV co-infection increase the risk of anti-TB-DIH [28, 66]. A study on 128 patients in Florida, showed that approximately 30% of HCV infected individuals developed anti-TB-DIH compared with 11% among uninfected individuals and HCV infection was an independent risk factor for the development of hepatotoxicity [52].

6.5. HIV/AIDS

HIV infection increases the risk of hepatotoxicity during standard multidrug treatment of TB [18]. Marzuki et al. (2008) found that HIV was a significant independent risk factor for developing anti-TB-DIH [58]. Similarly, Ungo et al. (1998) observed that infection with HIV is responsible for increased risk of anti-TB-DIH [52]. HIV patients with acute illnesses have altered activities of oxidative pathways, which may partly explain their increased risk of anti-TB-DIH [67]. Concurrent therapy of TB/HIV co-infection requires concomitant use of two to four different

anti-TB drugs and at least three antiretroviral drugs. Unfortunately, combined TB/HIV treatment is often complicated by overlapping toxicities and drug–drug interactions [68]. The simultaneous use of antifungals (e.g. fluconazole) in HIV-infected patients, is also a risk factor for anti-TB-DIH [69]. Increased risk of anti-TB-DIH in HIV patients may be related to an underlying viral replication or the immunocompromised state [19]. Severe TB infection in HIV-infected patients may be one of the reasons for their higher risk of anti-TB-DIH [20].

6.6. Anti-TB-DIH and oxidative stress

Studies have shown that anti-TB-DIH is primarily due to oxidative stress, caused by the drugs and metabolites [70]. The role of oxidative stress in the mechanism of INH and RIF-induced hepatitis has also been reported by Attri et al. (2000) [71]. In experimental rats oxidative stress has been proved a major mechanism of hepatotoxicity due to anti-TB drugs [72]. According to Funde et al. (2013) oxidative stress due to free radical generation and subsequent lipid peroxidation of membrane play a critical role in the pathogenesis of drug induced liver injury [73].

Oxidative stress is an unbalanced state characterized by an increased production of reactive oxygen species (ROS) and decreased level of antioxidants. In the liver, hepatotoxic metabolites of anti-TB drugs induce increased ROS generation that activates intracellular antioxidant defence mechanisms including antioxidants such as glutathione (GSH) and superoxide dismutase (SOD). The altered levels of antioxidant enzymes critically influence the susceptibility of various tissues to oxidative stress and are associated with the development of liver complications. [Figure-4].

6.6.1. Reactive oxygen species (ROS)

ROS is a combined term that describes the chemical species, which are formed upon incomplete reduction of oxygen and includes superoxide anion ($\text{O}_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^{\cdot}), that have a greater chemical activity than molecular oxygen [74]. Mitochondrion is a major intracellular

source of ROS. The mitochondrial electron transport chain contains several redox centers, which may leak electrons to molecular oxygen, serving as the primary source for $O_2^{\bullet-}$ production in most tissues [75]. This $O_2^{\bullet-}$ production occurs primarily on the matrix side of the inner mitochondrial membrane [76]. Mitochondrial $O_2^{\bullet-}$ is dismutated to H_2O_2 by Mn-SOD and in the presence of metal ions, highly reactive HO^{\bullet} is generated via fenton and /or Haber-Weiss reactions, inflicting significant damage on cellular proteins, lipids and DNA [77].

Another major source of ROS, especially in the liver, is a group of enzymes called the cytochrome P450. These are membrane bound terminal oxidases present mainly in the Endoplasmic Reticulum as components of a multi-enzyme system [78]. These, active cytochromes produce ROS, namely $O_2^{\bullet-}$ and H_2O_2 [79] and are therefore, considered a significant source of ROS. Other intracellular sources of ROS are peroxisomes, activated macrophages and neutrophils. The exogenous sources of ROS are xenobiotics, radiation and environmental toxins.

6.6.2. Lipid peroxidation

Excess production of ROS induces lipid peroxidation, which is considered as the main molecular mechanism involved in the oxidative damage and in the toxicity process that destroys cell structures, lipids, proteins and nucleic acids [80]. Lipid peroxidation is a chain reaction initiated by the hydrogen abstraction by an oxygen radical, resulting in the oxidative damage of polyunsaturated fatty acids (PUFA), which are important components of the membrane surrounding cells and cellular organelles.

Highly reactive free radicals (R^{\bullet}) derived from xenobiotics start a chain reaction by abstracting hydrogen atom from PUFA, result to the formation of a lipid radical ($PUFA^{\bullet}$), which further react with oxygen yield the corresponding peroxy radical ($PUFAOO^{\bullet}$) and chain propagation arises. This ultimately results in membrane disruption, formation of reactive aldehydes, and depletion of cellular storage of reduced GSH [81, 82]. [Figure-5].

Therefore, lipid peroxidation has been implicated in the pathogenesis of many types of liver injury, induced by several toxic substances. Increased lipid peroxidation due to production of reaction metabolites during the metabolism of anti-TB drugs has also been reported by Chawdhry et al. (2001) [83].

6.6.3. Antioxidants (GSH and SOD)

The implication of oxidative stress in the pathogenesis of anti-TB-DIH is suggested, not only by free-radical generation, but also due to alteration in antioxidant enzymes that play an important role in elimination of free radicals.

GSH an antioxidant, is a critical component of defence mechanism, and is found in cells and biological fluids throughout the body. In its reduced form, GSH acts as an antioxidant by reacting directly with ROS to neutralize them and gets oxidized (GSSG) by the combination of two GSH molecules. The body is able to rapidly convert GSSG back to GSH using NADPH (reduced nicotinamide adenine dinucleotide phosphate) as reducing source. However, during exposure to large amount of ROS, NADPH can become depleted, leading to an accumulation of GSSG and a depletion of GSH [84]. Therefore, decreased level of GSH may be an indicator of oxidative stress. According to Chawdhry et al., (2001) the reduction of glutathione during anti-TB drug treatment in patients developing hepatotoxicity, indicates its participation in an attempt to provide protection against liver injury [83].

SOD is also a naturally occurring antioxidant enzyme that protects the body against active oxygen free radicals and cell destruction by scavenging and neutralizing excess superoxide free radicals. SOD contributes an important role in the body's defence mechanism by catalyzing dismutation of the most reactive superoxide free radicals (the most reactive form of oxygen and the most dangerous for cell) into H_2O_2 that are less reactive. If these defence mechanisms do not immediately eliminate the free radicals, the body's cells suffer from an oxidative stress that can promote health problems. There are three forms of SOD: the manganese containing SOD (Mn-SOD) which is located in the mitochondrial

matrix, and the more ubiquitous SOD containing copper and zinc (Cu-Zn-SOD) located in the cytosol, the extracellular space and the mitochondrial inner membrane. The third form and the so-called extracellular SOD (EC-SOD) is present on the surface of the cells and also contains a copper-zinc prosthetic group [85].

6.7. Genetic risk factors

CYP2E1 and *GSTs* are the two main enzymes, which play a significant role during the metabolism of anti-TB drugs. Genetic variations in these drug metabolizing enzymes might modulate the pathway of drug metabolism and induce the toxic effects of drugs in terms of liver injury [86, 87]. Therefore, the genetic polymorphism of these genes may be an important risk factor for the development of anti-TB-DIH.

6.7.1. CYP2E1

Human *CYP2E1* gene is located on the 10th chromosome, consists of 9 exons and 8 introns, contains a typical TATA-box and occupies 11,413 base pairs of genomic DNA [88]. *CYP2E1* is constitutively expressed primarily in the liver [89] and its expression level is significantly lower in other organs and tissues, in particular, kidneys, pancreas, brain, lung, nasal and intestinal mucosa [90, 91]. *CYP2E1* is a membrane-bound protein with molecular weight of ~ 57 kDa and consists of 493 amino acid residues and is primarily associated with Endoplasmic Reticulum membranes [92]. *CYP2E1* is involved in the metabolism of more than 80 low-molecular weight, hydrophobic toxic compounds and activation of many procarcinogens and drugs to highly reactive metabolites [93, 91]. *CYP2E1* possesses a unique ability to reduce molecular oxygen to highly reactive compounds such as superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^{\cdot}). Which lead to intensified lipid and protein peroxidation, DNA damage and carcinogenesis [89].

CYP2E1 is one of the most important phase I metabolic enzymes in the human body which has a key role in the production of hepatotoxic metabolites [86]. Among the first line anti-TB drugs, INH is the main drug to induce the risk of

anti-TB-DIH. Metabolic intermediates of INH, are incriminated as the cause of hepatotoxicity [94; 32] and the production of these hepatotoxic metabolites is directly associated with higher activity of *CYP2E1*. This enzyme has genetic polymorphism in humans. The three genotypes of this enzyme are classified as C1/C1, C1/C2 and C2/C2. *CYP2E1* C1/C1 genotype is reported to be responsible for higher *CYP2E1* activity than those with *CYP2E1* C1/C2 or C2/C2 genotype and is involved in anti-TB-DIH [95]. Huang et al, (2003) also reported significant association between *CYP2E1* C1/C1 genotype and risk of anti-TB-DIH [33]. In contrast to this study, other recent studies [96, 97] found no relationship between *CYP2E1* C1/C1 genotype and anti-TB-DIH in their Korean population. These results are inconsistent with those of Cai et al. (2012), who showed positive correlation between *CYP2E1* C1/C1 genotype and anti-TB-DIH [98]. A study including 318 subjects on anti-TB therapy showed that subjects with *CYP2E1* c1/c1 were 2.5 times more likely to develop hepatotoxicity when compared with the other genotypes [99].

6.7.2. GSTs

GSTs, a family of cytosolic enzymes, are ubiquitously distributed in nature and found in virtually every living species including plants, animals and bacteria, where they catalyze a variety of reactions and accept endogenous and xenobiotic substrates. *GST* isoenzymes are involved in the detoxification of various exogenous as well as endogenous reactive species. [100, 101]. *GSTs* catalyse the conjugation of reduced glutathione via a sulfhydryl group to electrophilic centers on a wide variety of substrates. This activity detoxifies endogenous compounds such as peroxidised lipids, as well as breakdown of xenobiotics [102]. *GSTs* may also function as transport proteins by binding with toxins. According to Ginsberg et al. 2009, *GSTs* play a key role in cellular detoxification, protecting macromolecules from attack by reactive electrophiles, including environmental carcinogens, reactive oxygen species and chemotherapeutic agents [103]. Therefore, the

level of *GSTs* expression is a crucial factor for determining the sensitivity of cell to toxic chemical.

GST isoenzymes have been assigned to eight separate classes, including Alpha, Mu, Kappa Omega, Pi, Sigma, Theta, and Zeta encoded by the *GSTA*, *GSTM*, *GSTK*, *GSTO*, *GSTP*, *GSTS*, *GSTT* and *GSTZ* genes, respectively [104, 105]. In addition, each class includes several genes and isoenzymes. Polymorphisms have been reported in the *GSTM1*, *GSTT1* and *GSTP1* genes coding for *GSTs* enzymes in the Mu, Theta and Pi classes, respectively [106].

The human *GSTM1* gene is located on chromosome 1p13.3. and has a common functional variant (null versus present) [107]. The frequency of this null varies between 23% to 63% depending on the population studied [108]. Individuals with homozygous deletion of this gene have no enzymatic functional activity of the cytosolic enzyme *GST* Mu. These genetic variations can change an individual's susceptibility to carcinogens and toxins as well as affect the toxicity and efficacy of certain drugs. The mu class of enzymes functions in the detoxification of electrophilic compounds including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione.

The human Theta class of *GST* gene is comprised of two subunits *GSTT1* and *GSTT2*, both of which are located on chromosome 22q11 [109]. The polymorphism in the *GSTT1* gene loci is caused by a gene deletion, which brings about the virtual absence of enzyme activity in person with the null genotype. Homozygous deletion of this gene (*GSTT1* null) have been reported in 20% of the Caucasian population, 25% of African Americans and 50% of Asians [110].

Therefore, individuals with homozygous deletions of either the *GSTM1* locus and/or the *GSTT1* locus have no enzymatic functional activity of the respective enzyme, and has greater sensitivity for toxic chemicals. Therefore, it has been proposed that the decreased production of *GSTM1* and *GSTT1*,

characteristic of the null genotypes, may be associated with an increased risk of anti-TB-DIH [98].

7. CONCLUSION

Anti-TB-DIH is the leading cause of severe liver injuries among patients with TB diseases and the most common reason for failure of TB cases. Articles used in this review shows that younger age, female sex, malnutrition, HIV, oxidative stress and genetic polymorphisms of drug metabolising enzymes play a noteworthy role in the pathogenesis of anti-TB-DIH. These risk factors associated with anti-TB-DIH may be imperative in screening among individuals at high risk for anti-TB-DIH and ultimately can refine DIH prevention efforts. Therefore, patients on anti-TB drug therapy should be counselled carefully for the early detection of hepatotoxicity.

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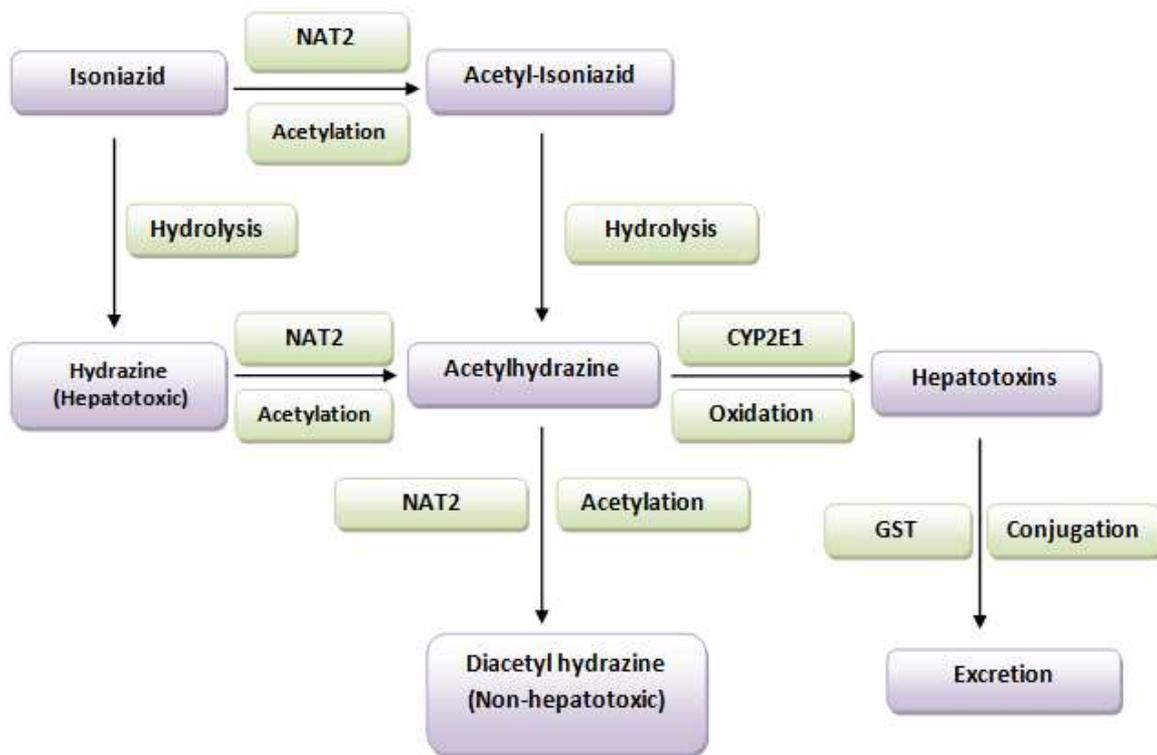


Figure: 1. Schematic representation of Isoniazid metabolism in Liver

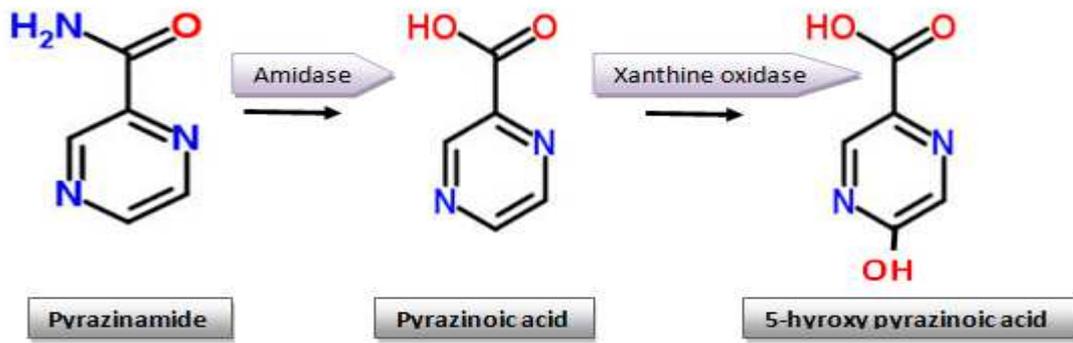


Figure: 2. Schematic representation of Pyrazinamide metabolism in Liver

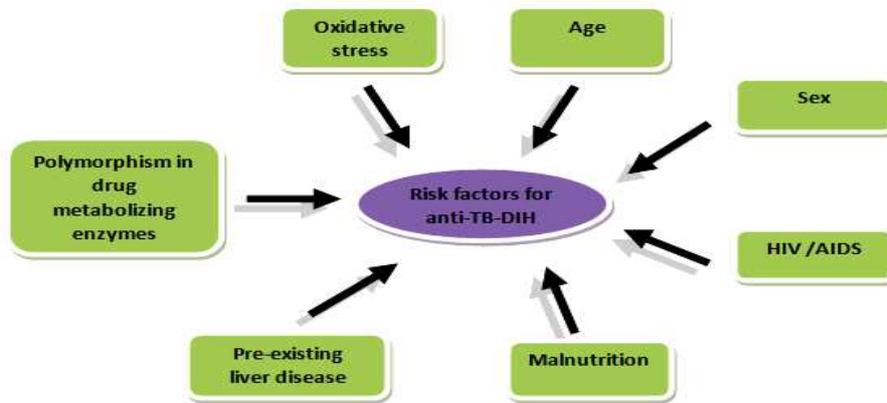


Figure: 3. Risk factors for anti-TB-DIH

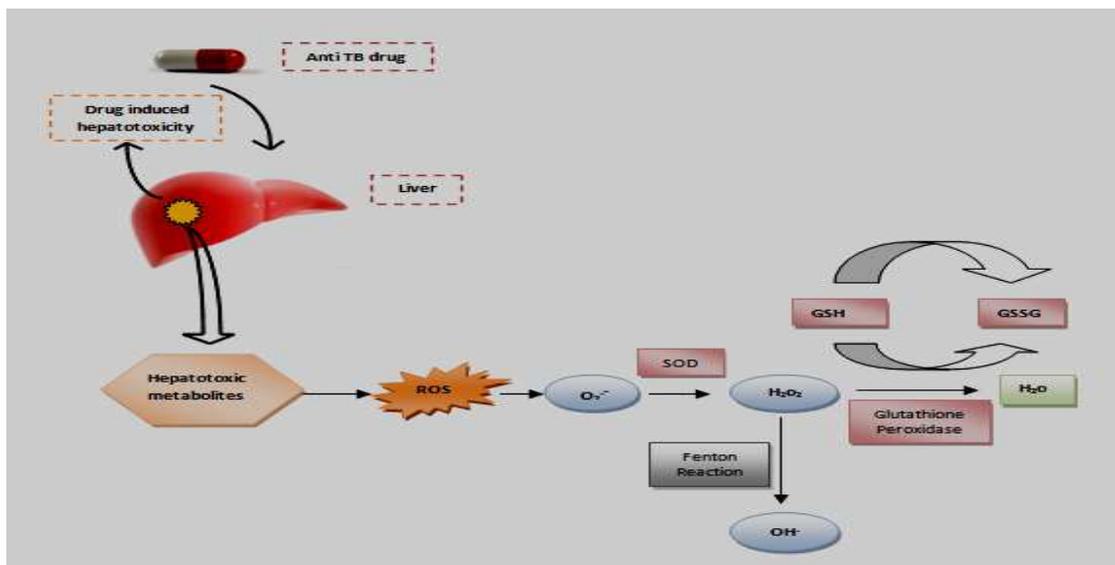


Figure: 4. Association between oxidative stress and anti-TB-DIH

In the liver, hepatotoxic metabolites of anti-TB drugs induce increased ROS generation ($O_2^{\bullet-}$, H_2O_2 and OH^{\bullet}) that activates intracellular antioxidants such as GSH and SOD. The altered levels of antioxidant enzymes critically influence the susceptibility of various tissues to oxidative stress and are associated with the development of liver toxicity

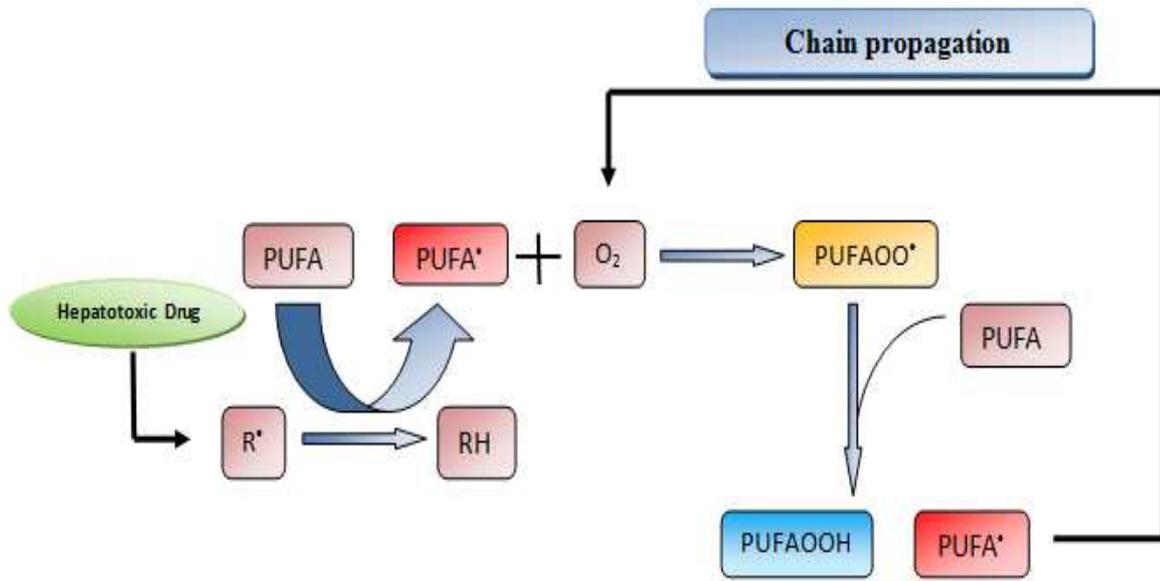


Figure: 5. Schematic representation of the process of lipid peroxidation

R^\bullet - Reactive free radicals; PUFA- Polyunsaturated fatty acids; $PUFA^\bullet$ - Lipid radical; $PUFAOO^\bullet$ -Lipid peroxy radical; PUFAOOH- Lipid hydroperoxide