



A REVIEW OF ANTITUBERCULOSIS DRUGS EMPHASISING ON PHYTOTHERAPEUTIC ASPECT

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Abstract

The long duration tuberculosis therapy makes causes several serious side effects, hepatotoxicity being the main. Hepatotoxicity is the most serious adverse effect related to tuberculosis treatment which interrupts the successful completion of tuberculosis treatment antioxidant system of the body effectively neutralises reactive oxygen species formed during the normal metabolic process. Any imbalance in this neutralization process causes oxidative stress leading to causation of various diseases. Research has enabled the use of several medicinal plants from time to time to treat toxic manifestations from various toxic substances. This review is aimed to provide an insight for the phytotherapeutic intervention of the medicinal plants for the effectiveness of the existing tuberculosis therapy.

Keywords: Tuberculosis, antituberculosis drugs, hepatotoxicity, medicinal plants.

Introduction

With the advent of modern scientific age, treatment for various diseases has been established in a sophisticated manner. However, in most of the cases, the therapeutic regimen is also responsible for causing secondary side effects, which directly or indirectly hamper functioning of various organs. These drugs have mostly been found to interact with the cellular biomolecules and thus cellular functioning is affected. The side effects are more prone in case the therapeutic regimen is too lengthy. Many of the approved drugs have been withdrawn from the market because of their adverse effect on liver. In western country, more than half of the cases of liver failure are because of the drug induced liver injury (DILI) and amongst them, paracetamol is found to be one of the main offending agents. The DILI has now become a clinical challenge because of large number of drugs with known hepatotoxicity are still in use and also because of broad spectrum of injuries that are caused to the liver by these drugs. Several drugs (e.g., astemizole, cisapride, grepafloxacin, terfenadine) have been withdrawn from clinical use as they have an effect on heart functioning. The antitumor drugs targeting the nuclear DNA exert their desirable toxic effects against tumor cells but besides that also exert their undesirable cytotoxic effects against rapidly dividing normal cells such as hematopoietic cells and small intestinal mucosal cells) by inducing apoptosis primarily via a p53-dependent mechanism. It is not surprising that most idiosyncratic drug reactions affect the liver, because this organ contains 80–90% of the body's fixed macrophages (i.e., Kupffer cells), because the liver is the first organ to be exposed to toxogenstranslocating from the intestinal lumen. Recently, an increase has been observed in the study of antituberculosis drug induced hepatorenal injury.

Tuberculosis

Tuberculosis (TB), a multisystemic disease is the most common cause of infectious disease related mortality worldwide. According to the World Health Organization (WHO, 2016) report, there were an estimated 10.4 million incident cases of TB in 2012 and 1.5 million deaths were attributed to the disease. The origin of genus mycobacterium is hypothesized to be originated some 150 million years ago

(Hayman, 1984). The disease is distinguished by a multitude of symptoms as cough, sputum production, chest pain, and systemic symptoms such as night sweats, fevers, chills, and weight loss.

The history of tuberculosis drug development began in the 1940s with streptomycin (1946). A decade later, the discovery of isoniazid (INH) brought new hope. In the 1970s, (PZA) and rifampin (RIF) revolutionized TB treatment, resulting in robust cures with shortened durations of therapy. Historically, no new drugs have been introduced in the clinic since the discovery of rifampin, in spite of major advances made in the drug discovery process.

The regimen for treating drug-susceptible TB involves six month treatment with isoniazid, rifampin, pyrazinamide and ethambutol (EMB) for first 2 months followed by INH and RIF for 4 months (Koul *et al.*, 2011). Currently available treatment regimens are prolonged, making the adherence to the therapy difficult. The occurrence, risk factors, morbidity and mortality of adverse events from isoniazid and rifampin have been well documented (White *et al.*, 2012). Also Shih *et al.* (2012) proposed a novel mechanism which underlies the hepatotoxicity of pyrazinamide. Hepatotoxic effects decline treatment success rates, adversely affect therapy adherence and may escalate treatment failure, relapse, or drug resistance. Incomplete chemotherapy in long run may directly or indirectly result into multi-drug resistant (MDR) strains, extensively drug resistant (XDR)-TB or even total drug resistant (TDR) strains.

Antituberculosis drugs

Even though the causative agent of tuberculosis (TB) was first identified by Robert Koch over 100 years ago, the epidemic still continues. The TB remains a huge global public health problem with much of the burden felt by developing countries in south-east Asia, Africa and Eastern Europe. The reasons for continuing TB epidemic may include devastated health care systems in resource-poor countries and insufficient diagnostic tools. Most TB-affected populations are concentrated in poorer regions of the world and fatalities occur excessively in Africa. The chemotherapy for this disease is available in the form of first line (Isoniazid,

Rifampicin, Pyrazinamide and Ethambutol) and second line drugs.

These first line drugs have been attributed to cause several serious side effects affecting various body organs. In general 50% of patients treated with isoniazid have adverse events such as peripheral neuropathy and hepatotoxicity.

Prior to the advent of the first antibiotic, treatment of TB involved a long journey. Then the first antibiotic streptomycin that was successful in treating TB infections was discovered in 1945 (Pyle, 1947). Streptomycin was the first drug used for the treatment of tuberculosis (Waksman, 1969; Pfuetez *et al.*, 1955). It was isolated in 1944 by Selman Abraham Waksman and he was awarded the Nobel Prize for this discovery in 1952. Two years later, in 1946, para-amino salicylic acid (PAS) as an effective TB drug was found to be effective for treating TB, especially in combination with streptomycin. This was followed by the highly active TB drug isoniazid in 1952 representing even better activity against *M. tuberculosis* than either of the two drugs i.e., para-aminosalicylic acid or streptomycin. This also enables to establish a base of the first three-drug treatment of TB (Pansy *et al.*, 1952). Later on many other potent drugs such pyrazinamide (1954), cycloserine (1955), rifampicin (1959) and ethambutol (1961) were introduced as anti-TB agents. Ethambutol and pyrazinamide replaced para-aminosalicylic acid and streptomycin by the 1980's and rifampicin had been introduced as well, giving the core first-line multidrug treatment for TB still used today. In cases of drug resistance, second-line drugs are utilized. These second line drugs include the aminoglycosides (including streptomycin), fluoroquinolones (e.g. ciprofloxacin), capreomycin and the macrolides.

The current anti-TB drugs target a limited range of cellular processes, namely cell wall biosynthesis, DNA replication, transcription, translation, and folate biosynthesis. Discovery of drugs that can inhibit novel targets is crucial for improving the current treatment regimens of TB, particularly drug-resistant TB (Duncan, 2003). The anti-tuberculosis drugs are classified as first line, second line and third line drugs based on their efficacy, side effects, toxicity, availability and cost. The first-line antituberculosis drugs are streptomycin, rifampicin, ethambutol, isoniazid and pyrazinamide. If the treatment fails, because of the bacterial resistance or intolerance to one or more drugs, second line drugs are used

Liver the metabolic machinery

The liver is the largest organ in the body and serves many essential functions such as digestion, produces bile, clotting factors, stores vitamins, minerals, protein, fats and glucose from diet, removes damaged red blood cells from the blood in co-ordination with spleen. The most important task of the liver is to filter toxic substances from the body, like alcohol, chemotherapeutic drugs, antibiotics and toxicants. Hepatic damage may occur if accumulation of toxins is faster than the liver metabolizing ability; the liver is placed between alimentary tract and the systemic circulation to maximize processing of absorbed nutrients and to minimize exposure of the body to toxins and foreign chemicals. Consequently, the liver may be exposed to large concentrations of exogenous substances and their metabolites.

Drug metabolizing enzymes (DMEs) play vital roles in the metabolism, elimination and/or detoxification of xenobiotics or exogenous compounds introduced into the body (Meyer, 1996). In general, DMEs protect the body against the potential harmful effects of xenobiotics as well as certain endobiotics. Phase I DMEs consist principally of the cytochrome P450 (CYP) superfamily of microsomal enzymes, which are found abundantly in the liver, gastrointestinal tract, lung and kidney. This superfamily consists of families and subfamilies of enzymes that are categorized based on their amino acid sequence identities or similarities (Guengerich, 2003). Phase II enzymes have a special role in the metabolic inactivation of pharmacologically active substances as well as biotransformation of endogenous compounds and xenobiotics to more excretable forms.

ATDs and mycobacterium

Isoniazid also known as isonicotinylhydrazide, is an antibiotic which is one of the main components of the first line tuberculosis therapy. The brand names of the isoniazid are Hydra, Hyzyd, Isovit, Laniazid, Nydrasid, Rimifon, and Stanozide. Isoniazid is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if the mycobacteria are slow growing (Ahmad *et al.*, 2009).

Mycobacterial cell wall is made up of mycolic acid and Isoniazid acts as an inhibitor of mycolic acid biosynthesis thereby impairing the cell wall biosynthesis. Specifically, isoniazid inhibits the fatty acid synthase II (FASII) enoyl-acyl carrier protein reductase (InhA). Isoniazid was first shown to have anti-TB activity in 1952, and was far superior to any agents in use at the time (Bernstein *et al.*, 1952). InhA was first identified in the isoniazid mode of action when a catalase positive mutant resistant to isoniazid was identified carrying mutations in *inhA* (Banerjee *et al.*, 1994). Subsequently it was found that isoniazid is a pro-drug that is activated by KatG into a reactive species that reacts with nicotinamide adenine dinucleotide (NAD) to form the isoniazid-NAD (INH-NAD) adduct responsible for inhibition of InhA (Rozwarski *et al.*, 1998; Wilming and Johnsson, 1999).

Rifampicin is a transcriptional inhibitor which binds to the β subunit of the DNA dependent RNA polymerase enzyme (RpoB) in bacteria (Wehrli *et al.*, 1968), including mycobacteria (Levin and Hatfull, 1993) thereby inhibiting the transcription. Rifampicin is a semi-synthetic drug derived from the natural product rifamycin. This derivative was found to have improved activity against gram-negative bacteria and the actinobacteria including mycobacteria. Clinical resistance to rifampicin is almost entirely due to mutations in *rpoB*, with 96% of mutations in rifampicin-resistant clinical isolates occurring within an 81 base pair (bp) sequence of the gene (Ramaswamy and Musser, 1998).

Pyrazinamide is a prodrug that needs to be converted into its active form, pyrazinoic acid, by bacterial enzymes (nicotinamidase/ pyrazinamidase). The mechanism of action of pyrazinamide has yet to be fully understood. It is supposed that pyrazinamide enters the bacillus passively, is converted into pyrazinoic acid by pyrazinamidase, and reaches high concentrations in the bacterial cytoplasm due to an inefficient efflux system. The accumulation of pyrazinoic acid decreases the intracellular pH to levels that cause the inactivation of enzymes such as fatty acid synthase I, which plays a

fundamental role in synthesizing fatty acids and, consequently, the impairment of mycolic acid biosynthesis. Resistance to pyrazinamide results from mutations in the *pncA* gene, which encodes the nicotinamidase/pyrazinamidase enzyme and prevents pyrazinamide from being converted into its active form.

Antituberculosis drugs and liver

(i) Isoniazid

The isoniazid is cleared mostly by the help of enzyme N-acetyl transferase 2 (NAT-2) in liver by acetylation. Resulted acetyl-isoniazid is metabolized primarily to monoacetyl hydrazine (MAH) and to the diacetyl hydrazine (nontoxic) besides some other minor metabolites (Huang *et al.*, 2002). The rate of acetylation has a genetic basis, as genetic polymorphisms of the specific enzyme NAT-2 link with fast, slow, and intermediate acetylation phenotypes (Huang *et al.*, 2003). Isoniazid intermediates are further being metabolized through phase I pathways by microsomal enzymes e.g., cytochrome P450 2E1. (Huang *et al.*, 2003). Mostly reactive metabolites of MAH are toxic to tissues through free radical generation. Acetyl-hydrazine; one of the resultant isoniazid metabolite covalently binds to liver macromolecules, a process mediated by microsomal enzymes.

Isoniazid inhibits the activity of several cytochrome P450 2E, thereby elevating concentrations of other potentially hepatotoxic drugs (Desta *et al.*, 2001; Tanaka *et al.*, 2000). Rifampin appears to promote the formation of toxic isoniazid metabolites in patients receiving isoniazid by enhancing a metabolic hepatocellular idiosyncratic reaction, perhaps by (Sarma *et al.*, 1986).

Shortly after its introduction to the market in 1952, INH was recognized to be associated with rare cases of liver injury. INH is placed among the top-ranking drugs regarding their potential to cause drug-induced liver injury (DILI), although the absolute numbers of INH-related DILI cases are smaller than those of other drugs that are given to much larger patient populations. Despite extensive research over several decades, the underlying mechanisms of INH-induced DILI have remained poorly understood. One of the reasons is the complexity of these mechanisms and the difficulty to distinguish between drug-related mechanisms (that determine the hazard) and patient-related mechanisms (that determine the actual risk).

The administration of INH and RIF produces a number of metabolic and morphological aberrations in the liver since liver is the main detoxifying site for several drugs including these ATDs. Several studies have shown that RIF increases INH toxicity by increasing the formation of its toxic metabolite hydrazine. Rifampicin induces cytochrome P450 enzyme causing an increased production of toxic metabolites from acetyl hydrazine (AcHz). Rifampicin also increases the metabolism of Isoniazid to isonicotinic acid and hydrazine, both of which are hepatotoxic. The plasma half-life of AcHz is shortened by Rifampicin and AcHz is quickly converted to its active metabolites by increasing the oxidative elimination rate of AcHz, which is related to the higher incidence of liver necrosis caused by INH and RIF in combination (Hussain *et al.*, 2012). The combination of INH and RIF is reported to produce higher rate of inhibition of biliary secretion, an increase in liver cell lipid peroxidation and cytochrome P450.

These parameters are supposed to have addition effects on hepatotoxicity of RIF on INH. The serum levels of hepatic enzymes and bilirubin are considered as diagnostic indicators for hepatic injury. An increase in the levels of these hepatic marker enzymes in serum is reported due to the leakage of these enzymes from liver as a result of tissue damage (Hussain *et al.*, 2012).

(ii) Rifampin

Rifampicin, also known as rifampin, is an antibiotic used to treat several types of bacterial infections. This includes tuberculosis, leprosy, and Legionnaire's disease. Common side effects include nausea, vomiting, diarrhea, and loss of appetite. A red or orange color of urine, sweat, and tears is a result of its consumption. It was introduced in the 1960s as a first-line anti-tuberculosis drug and became the most vital component of short-course chemotherapy in the 1970s. Rifampicin acts through the P 450 enzymatic pathway which makes its interaction with other drugs an important consideration in planning maintenance therapy (Ali, 1996). The metabolism of rifampicin is mediated via the deacetylation producing more water soluble compounds which are excreted through the biliary system (Ali, 1996).

Rifampin is often attributed to the induction of CYP3A4, which is the major CYP involved in the oxidative metabolism of various metabolites. It can be treated as an enhancer of the toxicity induced by the metabolism of isoniazid. So in combination with isoniazid, it is responsible for more toxic effects than isoniazid alone. Besides that gastrointestinal side effects including anorexia, and vomiting, hepatitis, nausea and reduced effectiveness of oral contraceptive pill can be linked to the use of rifampin.

Rifampin occasionally can cause hepatocellular injury and potentiate hepatotoxicities of other anti-TB medications (Menziez *et al.*, 2004). Rifampin may occasionally cause dose dependent interference with bilirubin uptake, resulting in unconjugated hyperbilirubinemia or jaundice. This may be short-lived and occur early in treatment or in some individuals with pre-existing liver disease (Erdil *et al.*, 2001).

Rifampin inhibits the major bile salt export pump thereby resulting in conjugated hyperbilirubinemia (Byrne *et al.*, 2002).

Elevated bilirubin may also result from impeded secretion at the canalicular level or dose-dependent competition with bilirubin for clearance at the sinusoidal membrane (Chitturi *et al.*, 2002). Hypersensitivity reactions have been found besides renal dysfunction, hemolytic anemia, or "flulike syndrome" (Martinez *et al.*, 1999, Covic *et al.*, 1998).

Rifampin leads to activation of hepatocyte pregnane X receptors thus subsequently to induction of cytochromes. Rifampin is also responsible for induction of uridine diphosphate-glucuronosyl-transferases and P-glycoprotein transport, subsequently affect the metabolism of other drugs (Burk *et al.*, 2004; Rae *et al.*, 2001). Rifampin also interacts with various drugs metabolized by these and other hepatic enzymes, including prednisone, warfarin, digitoxin, ketoconazole, itraconazole, quinidine, propranolol, sulfonyleureas, clofibrate, phenytoin, HIV protease inhibitors, and HIV nonnucleoside reverse transcriptase inhibitors (Niemi *et al.*, 2003).

(iii) Pyrazinamide

Pyrazinamide may cause dose dependent and idiosyncratic hepatotoxicity. Pyrazinamide alters nicotinamide acetyl dehydrogenase levels in rat liver (Shibata *et al.*, 2001), which might result in generation of free radical species. Pyrazinamide is also responsible for the toxic manifestations but the exact mechanism of the toxicity generation is yet to be fully elucidated. Joint pains have also been a result of the pyrazinamide. Shared mechanisms of injury may be there for isoniazid and pyrazinamide, as there is some sort of similarity in molecular structure. Patients who previously had hepatotoxic reactions with isoniazid have had more severe reactions with rifampin and pyrazinamide given for latent tuberculosis infection (CDCPA, 2001). Hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis may be a result of pyrazinamide use (Knobel *et al.*, 1997).

Pyrazinamide has been used with rifampin, ethambutol, or a fluoroquinolone for treatment of latent tuberculosis infection. Transaminase elevation was seen in most of the LTBI cases treated with pyrazinamide and ethambutol (Younossian *et al.*, 2005). Because the fluoroquinolones and ethambutol alone rarely cause hepatotoxicity, pyrazinamide is believed to be the offending agent in most cases of hepatotoxicity associated with these regimens.

The half-life of pyrazinamide is comparatively longer than that of either isoniazid or rifampin, approximately 10 hours (Huang *et al.*, 2003). Half-life is increased to 15 hours in patients with preexisting hepatic disease, (Lecroix *et al.*, 1990). Pyrazinamide, a nicotinic acid derivative, converted to pyrazinoic acid by pyrizonic acid in the liver and subsequently metabolized to 5-hydroxy-pyrazinoic acid by xanthine oxidase (Lecroix *et al.*, 1990), xanthine dehydrogenase (Nasu *et al.*, 1981) and aldehyde oxidase (Moriwaki *et al.*, 1993). Besides this, 5-hydroxy-pyrazinamide may also be generated during metabolism.

(iv) Ethambutol

There has been one report of ethambutol-related liver cholestatic jaundice, with not so clear circumstances (Gulliford *et al.*, 1986). Because of the potentially serious nature of this complication, there has been considerable reluctance to use EMB in young children, and most international guidelines recommend that EMB should not be given to children less than 5 or 7 years of age. However, there is a substantial body of published literature confirming to the use of EMB in young children.

Ethambutol can cause irreversible visual loss in a small but significant fraction of patients. The incidence of ethambutol-induced optic neuropathy has been reported to range from 1.0% to 22% (Rizzo, 1993), depending on the dosage. Ethambutol-induced neuroretinopathies including retinal pigment epithelial changes, macular edema, retinal hemorrhage, and abnormal electrophysiological properties, have also been reported, but with a lower frequency than ethambutol induced optic neuropathy (Vistamehr *et al.*, 2007). Although vision loss is often reversible when ethambutol is discontinued, some patients suffer permanent vision loss, even with standard dosages of ethambutol (Alvarez and Krop, 1993; DeVita *et al.*, 1987). However, the pathophysiology of ethambutol-induced ocular toxicity remains unclear.

Fluoroquinolones

Some of the fluoroquinolones like ciprofloxacin and moxifloxacin are metabolized, in part, by the liver, while as other drugs such as gatifloxacin, levofloxacin, ofloxacin are largely excreted by the kidneys. Serious hepatocellular injury and cholestasis have been reported in less than 1% of all fluoroquinolone recipients (Dombeck *et al.*, 2001; Lazarczyk *et al.*, 2001). Reversible transaminase increase among the fluoroquinolone recipients may occur in up to 2 to 3% of cases (Bertino *et al.*, 2000). Ciprofloxacin, trovafloxacin, norfloxacin, ofloxacin, enoxacin, levofloxacin, and gatifloxacin has been reported to pose a significant hepatotoxicity (Coleman *et al.*, 2002; Kahn *et al.*, 2001). The rate of severe hepatotoxicity for levofloxacin was reported to be less than 1 per 1,000,000 (Kahn *et al.*, 2001). According to Coleman *et al.*, 2002, the mechanism of fluoroquinolone hepatotoxicity is a manifestation of hypersensitivity reaction, often displayed by eosinophilia (Coleman *et al.*, 2002). Regarding hepatotoxicity between cases treated with pyrazinamide and fluoroquinolone, the causative agent has most often been assumed to be the first (Saigal *et al.*, 2001; Younossian *et al.*, 2005).

Phytotherapeutic alternative

To overcome this problem, number of herbal treatments have been experimented and used throughout the world. India is well known for its plant biodiversity and thousands of plants or plant products remain the integrated part in human civilization. Traditional medicine systems including *Ayurveda*, *Unani* etc. have been backbone of medicinal wealth. Human health has mainly dependent upon the plants throughout ages.

Plants have been utilized for their aromatic and medicinal properties for centuries with important implications due to their safety and availability profile. Over three-quarters of the world population rely mainly on plants for health care and only 30% of the entire plant species are currently used for medicinal purposes.

Modern era is blessed with many advancement of scientific research, whether it is in food science or pharmacognosy. Due to the use of some food items as well as synthetic medicines, human body is continuously exposed to a kind of oxidative stress. Oxidative stress might be an important part of many human diseases; the use of antioxidants in pharmacology is intensively studied. Antioxidants are widely used as ingredients in dietary supplements in the hope of maintaining health and preventing diseases. Various plants have been observed and reported from several years for their presence of antioxidants. Tasduq *et al.* (2005) used 50% hydroalcoholic fruit extract of *Emblica officinalis* against anti-tuberculosis drugs induced liver toxicity to know its protective effects. After a couple of years Kalra *et al.* (2007) analysed the effect of cimetidine on hepatotoxicity induced by isoniazid-rifampicin combination in rabbits. Similarly antihepatotoxic effect of *Picrorhiza kurroa* on mitochondrial defence system in antituberculosis drugs (isoniazid and rifampicin)-induced hepatitis in rats was assessed by Jeyakumar *et al.*, 2008. Hussain *et al.*, (2012) studied the toxic manifestations of anti-tuberculosis drugs and the therapeutic effects of *Solanum xanthocarpum* against the same. Subsequently a similar kind of study was carried out by Jaswal *et al.*, 2013, who used thymoquinone as a therapeutic agent against anti-tuberculosis drugs induced

toxic manifestations. Other plants were used also for hepatoprotective purposes; *Andrographis paniculata* is such health food used mainly in Southeast Asia, India and China and contains the pharmacologically important phytochemical andrographolide. Andrographolide has antihepatotoxic activity; its bioavailability from *A. paniculata* is restricted by its rapid clearance and high plasma protein binding. (Maiti *et al.*, 2010). *Tephrosia purpurea* is one amongst the vital medicinal alternatives also. It is a common wasteland weed, which grows in poor soils and found throughout India. Besides antibacterial potential (Malik *et al.*, 2017) it has a myriad number of essential medicinal properties. So it could also be investigated for the therapeutic purpose.

Conclusion

Due to the emergence of multi-drug resistance pathogenic bacteria as well as undesirable side effects of certain antibiotics have triggered immense interest in the search for new antimicrobial drugs of plant origin. A diverse number of medicinal plants are there in the nature with a strong potential to cure many ailments owing to their antioxidant properties. So a perfect effective therapy can be proposed against tuberculosis using phytotherapeutic alternative.

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