Review: Treatment of toxicity caused by anti-tubercular drugs by use of different herbs

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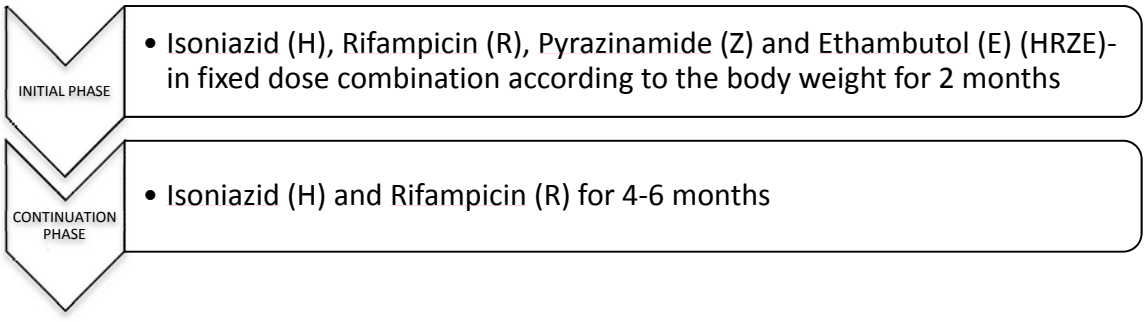
ABSTRACT

Tuberculosis is a familiar ailment in India and worldwide and is chief cause of mortality among all the infectious diseases. In present scenario therapy of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol are commonly recommended against TB. These drugs lead to many adverse reactions which are one of the major reasons for non adherence of patients to these drugs that may lead to development of MDR. With the current scenario of MDR cases rising, this problem of adverse drug reactions cannot be taken lightly. Due to lack of successful drugs for treatment of toxicity caused by anti-TB drugs we have to turn towards traditional medicine. Ayurveda is an ancient system of natural and holistic medicine. Ayurvedic herbs have still being used as a part of treatment regimen in many parts of world. Local people still use these herbs as they are full of curative properties. Because anti-tubercular drugs induced toxicity leads to oxidative enzymes imbalance also leads to necrosis in liver tissue and many other degenerative changes, herbal extracts were experimented upon to test their ability to ameliorate toxicity by activating protective pathways. In this review we have summarized few of such herbs whose extracts were tested for their curative properties against anti-tubercular drugs induced toxicity. The main constituents in extracts that were responsible for protective effects have also been summarized along with their mechanisms of action.

KEY WORDS- Rifampicin, Isoniazid, Pyrazinamide, Herbs

INTRODUCTION

In developing countries like Africa and South-East Asia, tuberculosis which is caused by bacillus bacteria i.e. *Mycobacterium tuberculosis* is an epidemic as it is main cause of morbidity and mortality there. Control of an ever changing epidemic of TB is a true challenge in India, country that contributes more than a quarter of global cohort of TB patients and stands first among the 27 multidrug-resistant TB (MDR-TB) high burden countries [1]. Therefore there is an urgent need for proper management if this epidemic clinically. Principle TB treatment regimen involves the delivery of four drugs: Isoniazid (INH), Rifampicin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB) or Streptomycin (SM). Initial treatment with the mentioned first line drugs over 2 months leads to destruction of strains of mycobacteria in all growth stages. After this continuation phase consists of RIF and INH alone so that if there were any residual dormant mycobacterial strain remaining they should be eliminated [2, 3]. For latent tuberculosis, the standard treatment is six to nine months of Isoniazid alone. If bacteria become resistant to first-line drugs then only second-line drugs (e.g. capreomycin, cycloserine, kanamycin, ethionamide) have to be used which have major ill effects with 50% cure rate. Preferred regimen for TB treatment consists of two phases:



TOXICITIES ASSOCIATED WITH CURRENT THERAPY

Severe adverse reactions to anti-TB drugs are very common and result in utilization of substantial health care services along with lengthening of therapy. Adverse reactions to anti-tuberculosis drugs can cause prominent morbidity, even mortality and results in discontinuation of the drug. HIV-infected individuals, older and Asian-born patients are at more risk [4]. Side effects to these drugs include hepatitis, cutaneous reactions,

gastrointestinal intolerance, hematological reactions and renal failure [5], ocular reactions [6]. Oxygen reactive radicals are formed due to anti-TB drug administration which leads to lipid peroxidation and development of oxidative stress [7]. Oxidative stress further leads to damaging all the intracellular macromolecules such as glutathione, RNA, DNA, lipids, proteins and ATP. Disturbance in the level of these antioxidants and other molecules are of key importance in operating cellular functions and any changes in these, results to cell damage and apoptosis [8, 9].

Table 1- Showing side effects caused due to Anti-TB drugs [10]

S.NO.	DRUG	SIDE EFFECTS ASSOCIATED
1.	**Rifampicin**	nausea, dyspepsia, heartburn, anorexia, vomiting, flatulence, cramps, esophagitis, pseudomembranous colitis, Hyperbilirubinemia, hepatitis, Jaundice, hyperbilirubinemia,flu-like syndrome, itching and rashes, headache, paresthesias, weakness, , fatigue, ataxia, dizziness, decreased concentration, mental confusion, behavioral changes, muscular weakness, pain, and numbness, pruritus, urticaria, rash, , pemphigoid reaction, drowsiness, erythema multiforme including Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, eosinophilia, sore mouth, sore tongue, and conjunctivitis, menstrual disturbances and adrenal insufficiency.
2.	**Isoniazid**	uncontrollable seizures, Peripheral neuropathy, visual disturbances, ataxia, Hepatitis, jaundice, anemia, Agranulocytosis, thrombocytopenia, and eosinophilia, drug fever, rash, lymphadenopathy, vasculitis, urticaria, lupus-like reactions, Psychosis, depression, aggression, nausea, vomiting, epigastric distress, pyridoxine deficiency and pellagra
3.	**Pyrazinamide**	acute hypertension, granulomatous hepatitis, liver damage, increased uric acid, thrombocytopenia**,** Sideroblastic anemia with erythroid hyperplasia, vacuolation of erythrocytes, and increased serum iron concentration, rash, urticaria, pruritus, skin pigmentation, desquamation, and photosensitivity, nausea, vomiting, and anorexia, dysuria and interstitial nephritis
4..	**Ethambutol**	visual acuity, optic neuritis, Optic neuropathy, scotoma, color blindness, and visual defect , Hyperuricemia, liver toxicities, Jaundice, anaphylactic/anaphylactoid reaction, fever, cutaneous reactions (such as rash or exfoliative dermatitis), eosinophilia with or without drug-induced pulmonary infiltrates, hepatitis, pneumonitis, nephritis, pericarditis, lymphadenopathy, anaphylaxis, lichen-planus reactions, and toxic epidermal necrolysis, nausea, vomiting, abdominal pain, anorexia, and gastrointestinal upset, headache, dizziness, and numbness

MDR-TB- Resistance that develops due to anti-TB drugs is one of the toughest hurdles in the successful eradication of TB worldwide. Multi-drug resistant TB (MDR-TB) can be defined as resistance of *M. tuberculosis* bacteria to two major first-line TB treatment drugs; Isoniazid and Rifampicin with or without resistance to other drugs. Main reason for development of drug resistance is inappropriate use of TB drugs which are used in chemotherapy. This improper use can be due to number of reasons like administration of improper treatment regimens, failure to ensure that patients complete the whole course of treatment, sometimes due to non availability of drugs, Adverse reactions to anti-TB drugs is also one of major reason for development of MDR-TB as patient come across with so many side effects, this leads to poor adherence to the medication and stopping of drugs results in MDR-TB. Generally, drug resistance is seen in areas with weak TB control programmes. A patient has active disease with a drug-resistant TB strain can transmit it to others very easily.

COMBINATIONAL THERAPY AND DRUG INTERACTIONS

In case of anti-TB drugs combination therapy is used because the strain of bacteria that is causing disease may be resistant to one drug so it can be managed by another drug. However, these combinations can bring positive effects as well as negative effects to the health of the patients. Therefore, the drug interactions between the anti-tubercular drugs are considered before the drugs are prescribed to the patients as the drug interactions might influence the effectiveness of the tuberculosis treatment. According to studies done combined therapy was found more effective than monotherapy. When isoniazid was added to the therapy involving streptomycin and para-aminosalicylic acid, the effectiveness of the treatment increased [11]. Other than interacting among each other, anti-tubercular drugs will also interact with anti-retroviral drugs, also known as anti-HIV drugs. HIV is a virus which can cause AIDS in individuals. Nowadays, there are AIDS patients who are tuberculosis patients as well. However, there is difficulty in treating tuberculosis concomitantly with HIV. This is because there are drug

interactions between these two classes of drugs. An example of man retroviral drugs is the HIV protease inhibitors. Rifamycins which are a group of anti-tubercular drugs and it consist of rifabutin, rifapentine and rifampin. The presence of these anti-tubercular drugs in the serum of HIV patients with tuberculosis will lower the serum concentrations of HIV protease inhibitors. According to a study conducted, rifampin reacts with HIV protease inhibitors in such a way that it decreases the serum concentration of HIV protease inhibitors by 35% to 92% whereas rifabutin reduces the serum concentration of HIV protease inhibitors by 15% to 45% [12, 13, 14, 15]. The reduction of HIV protease inhibitor is so high that this condition cannot be overcome by the addition of HIV protease inhibitors [16]. The serum concentration of HIV protease inhibitors cannot be increased even by administering rifamycins intermittently [17]. Other than rifamycins, non-rifamycin anti-tubercular drugs can also interact with antiretroviral drugs. A study shows that co-administration of ethionamide with protease inhibitors can actually result in the increase in the serum concentrations of ethionamide and therefore, the toxicity increases [18].

HERBAL ALTERNATIVES

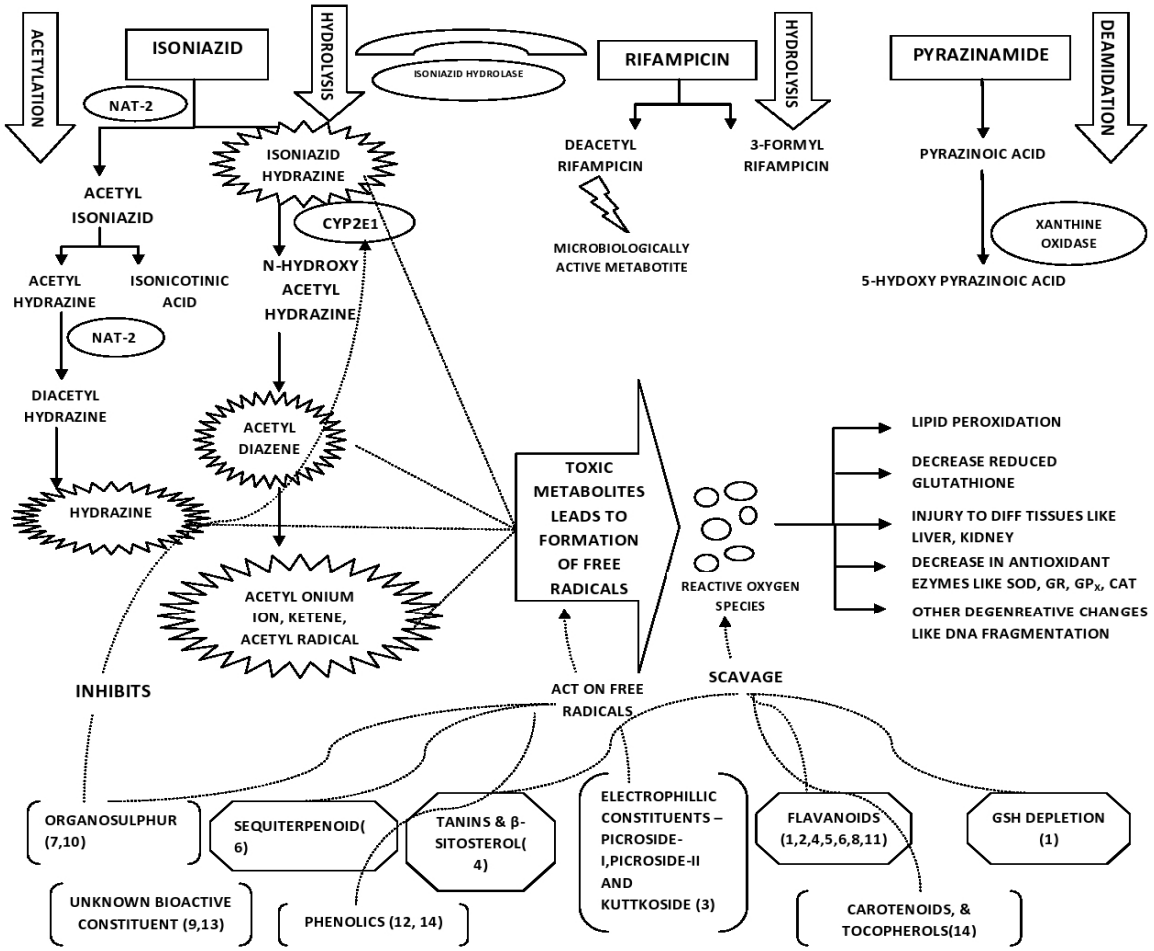
Herbs are doing a great comeback and herbal reawakening is happening all over the globe. In this era products made from herbs symbolize safety in contrast to synthetic products that are considered as unsafe to use for human and environment [19]. According to WHO 65% of world's population depends upon traditional medicine for primary health care. Of 300,000 higher plant species on earth more than 10,000 are medicinal. India is considered to be one of world's 12 biodiversity rich centers covering almost 45000 different plant species. In India drugs of herbal origin have been used in traditional system of medicines since long time like Unani and Ayurveda. The Ayurveda uses about 700 species, Unani-700, Sidha-600, Amchi-600 and modern medicine-30 species. Plant derived drugs not only offer a strong market worldwide but also herbs continue to be significant source of new drugs. Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several allopathic drugs and development of drug resistance to currently used drugs for infectious diseases has led to increases emphasis on use of plant materials as source of medicines for wide variety of human ailments. TB is such an infectious disease for which there is a need of development of such herbal supplement which can prevent the disease associated side effects. Here we are reviewing about herbs and their main bio-constituents, which were worked by different scientists against toxicity caused due to anti-tuberculosis drugs and in last decade (2004-14).

1. *Ginko biloba*- Naik and Panda worked on this herb of Chinese system of medicine. This is found to possess cardioprotective, anti-asthematic, anti-diabetic and has potent central nervous system activities [19]. Two major mechanisms that may be responsible for hepatoprotective activity of this plant are flavanoids which may be responsible for scavenging activity of reactive oxygen species that were produced due to toxicity caused by anti TB drugs and other mechanism is protection provided due to GSH depletion. Anti-TB drugs lead to formation of free radicals and this causes lipid peroxidation and causes the loss of membrane integrity and also causes damage to various organs like liver and kidney. Also during metabolism of anti-TB drugs they form toxic metabolites like hydrazine that cause all the harm.
2. *Annosa squamosa*- Other name is custard apple. It has many medicinal properties [21]. It is used as insecticidal agent has been investigated by several workers [22] free radical scavenging of this plant [23] was reported in leaf extracts. It also has hypoglycemic and antidiabetic [24-25], anticancerous properties. From this plant flavanoids [26] aporphine alkaloids [27] and squamoline [28] were isolated from this plant. In this plant flavanoids were thought to be the main biocontituent responsible for protective activity against anti tubercular drug induced toxicity [29].
3. *Picorhiza kurroa*- Rhizomes are used for viral hepatitis [30], traditional medicine for heart problems, abdominal pain, stomach diseases, anemia and jaundice. Isolated components [31] kutkin, kurrin, kutkrol, picroside I, picroside II, kutkoside, apocyanin,adrosin. Due to counteraction of free radicals by presence of electrophillic constituent, picroside II and kurkoside or to an activated conjugation of anti TB drugs with GSH in liver.
4. *Boerhaavia diffusa*- It is a perennial diffuse herb. Plant was found to contain alkaloids, flavanoids, glycosides, tannins, saponins, proteins [32] Tricontanol hentriacontane, B-sitosterol, sucrose, hypoxanthine 9 L-arabinoside, moulting horone ecdysone and many more active compounds were found to be present [33]. Muthulingam found that flavanoids and tannins also B-sitsterol have both antioxidant and anti-hypercholesterol properties and may be responsible for the protective activity of *Boerhaavia diffusa* against anttubercular drugs [34].
5. *Cassia fistula*- It is native plant of India and has properties like laxative, purgative, used in intestinal disorders, antipyretic and has analgesic effects. Leaf extract is also used for wound healing properties. It has phenolic compounds. Anti-tubercular protective action of this plant is due to presence of flavanoids present [35].
6. *Bombax cieba*- It is an essential medicinal plant of tropical and subtropical India. It is used for some diseases like inflammation [36], algesia, hepatotoxicity [37], hypertension as well for anti-angiogenic and

antioxidant activities [38]. Flavanoids and sequiterpenoids which scavage free radicals were thought to be reason for effectiveness of this plant against anti-tubercular drug toxicity [39] but this plant had mild protective effect it could not limit to the extent of necrosis.

7. *Apospora lindleyena*- It is a traditional medicinal plant. It was worked upon by Ramakrishnan and Venkatataramna [40]. This plant doesn't show any protective effect against the hepatotoxicity induced by the anti tubercular drugs.
8. *Cuscuta reflexa*- It is a yellow dodder like parasite plant. Various parts are used in diseases like fits, melancholy, inasanity. It acts as astringent to bowls, aphrodisiac, expectorant, carminative, tonic, purifies blood and cleanses the body. Not much is known about its bioactive constituents. Balakrishnan has done its protective effect over the anti tubercular drugs causing toxicity [41]
9. *Jasminum grndiflorum*- Its leaves are used for treatment of odontolagia, fixing loose teeth, ulcerative stomatitis, skin diseases, otalagia, stranguary, dysmenorrhoea, ulcers and wounds. It has flavanoids, phenolics, carotenoids, steroids, saponin and vitamin C [42]. Antioxidant properties were due to its bioactive constituents.
10. *Allum sativum*- Garlic is most popular herb used worldwide. Its constituents include steroids, terpenoids, flavanoids and other phenols. It reduces hyperlipedimia, reduces aortic plaques, inhibit cu^{2+} induced oxidative modification of low density lipoproteins. Mechanism of action of garlic is due to organosulphur compound in it [43]. Another study was done on garlic bulb by Ilyas [44]. garlic bulb contains g-glutamylcysteine. Consumption of garlic enhances the intracellular content of glutathione in all cells including those in normal liver and injured tissue. It has anti inflammatory effect also. It decreases cytokines like TNF-a, IL1, IL-6, IL-8, T cell interferon gamma, IL-2, and enhances the production and function of anti-inflammatory monocyte IL-10. Several enzymes of P_{450} are also inhibited thus decrease the production of toxic metabolic intermediates.
11. *Chayamansa*- Tree spinach, it is recommended for a number of ailments including diabetes, obesity, kidney stones, hemmoroids, acne and eye problems. Leaves contain constituents like K, Ca, Mg, Na, Fe, Mn, Zn, Cu, flavanoids like ametoflavone, astragatin, kaempferol-30, rutinoside and dihydrocyanic glycosides. Pillai thought there is a role of flavanoids in the protective activity against antitubercular drugs [45].
12. *Rhodomyrtus tomentosa*- called as Ceylon hill gooseberry is used in healing wounds and abcesses. In vitro antioxidant activity of this plant has been reported by different methods. This plant has presence of alkaloids, phenolics, flavanoids, saponins, carbohydrates, steroids and terpenoids. Geetha found out that phenolic compounds were responsible for the protective activity of this plant [46].
13. *Garcinia indica*- It is a slender evergreen tree, is endemic to west coast of India. It has many culinary, pharmaceutical and industrial uses. Many uses of fruits as an infusion for skin ailments such as rashes caused by allergy, appetizer, liver tonic, cardiotonic, tumors and heart diseases. One of its ingredient hydroxycitric acid another is garcinol is a poly-isoprenylated benzophenone is an antioxidant, a glyctioninhibitor, anti-ulcer ajent, anti-bacterial properties. Natural histone acetylasetransferase found to have antioxidant properties [47].
14. *Spirulina maxima*- It is a cyanobactrium algae. It contains nutrients like high protein, vitamin B complex, Minerals, g-linolenic acid, super antioxidants, B-carotene, vitamin E, trace elements. According to Jatav carotenoids, phenolics, tocopherols were responsible for antioxidant activity [48]

OTHERS- There are some other herbs which were also worked upon by scientists in last decade against the toxicity caused by anti tubercular drugs phenolic compounds present in plant were thought to be responsible for its protective effects. Ali worked upon three plants for their protective potential against anti tubercular drug toxicity [49]. *Mentha piperita*- being used for alleviating nausea, flatulence and vomiting. It was revealed that this plant has anti-oxidant properties [50-51].*Origanum vulgare*- source of phenolic antioxidants and has potential to be a source of nutritional ingredients for functional foods used in food preservation also [52]. *Pipinella anisum*- aromatic herb principle components are volatile oil, coumarins, fatty acids, flavanoids, glycosides, proteins, carbohydrates also it has anti microbial properties [53] among these three plants polyherbal preparartion of these herbs was most effective after that was *M.peprita* then was *O. vulgare* and least was *P.anisum*.



1. Ginko biloba, 2. Annosa squamosa, 3. Picorhiza kurroa, 4.Boerhaavia diffusa, 5. Cassia fistula, 6. Bombax cieba, 7. Apospora lindleyena 8. Cuscuta reflexa, 9. Jasminum grndiflorum, 10. Allum sativum, 11. Chayamansa 12. Rhodomyrtus tomentosa, 13. Garcinia indica, 14. Spirulina maxima

FIGURE 1: SHOWING THE MECHANISM OF ACTION OF ISONIAZID, RIFAMPPICIN AND PYRIZINAMIDE; THEIR TOXIC METABOLITES; BIOCONSTITUENTS THAT WERE FOUND RESPONSIBLE FOR PROTECTIVE EFFECTS OF DIFFERENT MENTIONED HERBS

CONCLUSION

Reason for development of anti-TB drug toxicity are mainly oxidative stress and cell damage, that happens due to the formation of free radicals that are formed from the toxic metabolites like hydrazine of anti-TB drugs. If we think about the solution of this problem it is somehow maintaining the level of anti-oxidant enzymes so that they don't damage the cells. As reviewed bioactive molecules of many herbs have anti-oxidative properties which can prevent development of ATT. These protective properties of these herbs can be beneficial in lot of diseases. Pre-clinical studies have proved the effectiveness of herbal extracts against ATT, however there is still a need of clinical studies in this field. Further elucidation of these bioactive molecules by using different techniques like HPLC/UPLC/MS and their testing against ATT is the need of the hour. At this stage what is required is more of pre-clinical and clinical trials so that strong data can be collected that can support the use of herbal extracts in treating ATT toxicity. Use of herbal extracts against ATT can be a powerful tool that can fight the problem of adverse reactions caused by TB treatment also this can help in controlling the MDR.

CONFLICT OF INTEREST-

The authors declare that they have no competing interests.

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