

Integrative Approach in Management of Antitubercular drug Induced hepatotoxicity

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Abstract

About one third of the world's population is suffering from latent TB and roughly 9 million cases of active TB emerge annually resulting in 2-3 million deaths. The most populated nations like India and China are on alarming bomb. Combination of four drug chemotherapy is recommended to attain a successful cure containing Isoniazid, Rifampicin and Pyrazinamide with or without ethambutol. But drug induced hepatotoxicity is a potential adverse effect associated with anti-tuberculosis treatment (ATT). To reduce the hepatotoxicity due to ATT, the popular measure is stoppage of causative drugs along with some vitamin supplementations.

The integrative approach to use medicinal herbal drugs mentioned in *Ayurveda* with proven hepato-protective activity may give solution of this problem. It is proved that some herbs are having activities like membrane stabilizing, anti-oxidative and CYP2E1 inhibitory effects against pathology of hepatotoxicity.

The critical study of classics of *Ayurveda* revealed that the herbs prescribed for Garavishajanya Vishaktata with *tiktarasa*, having action on *Raktavahasrotas* along with *Yakritagamitvam* may be used as hepatoprotective agent in the management of hepatotoxicity caused due to ATT. Preclinical and clinical studies are awaited to prove this hypothesis.

Key-words: Anti-tubercular drugs, *Adhatoda vasica*, *Azadirachta indica*, *Tricosanthes dioica*, *Terminallia chebula*, *Curcuma longa*, *Berberis aristata*.

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Introduction

Tuberculosis caused due to *Tubercle Bacillus* has been recognized as a clinical entity since the ages of Hippocrates (460-370BC). About one third of the world's population has latent TB¹ and this exhibits the magnitude and importance of the problem. Moreover, the most populated nations like India and China² are on alarming bomb. The recommended treatment regimen for Tuberculosis is the combination chemotherapy containing Isoniazid (INH), Rifampicin (RMP) and Pyrazinamide (PZA) with or without ethambutol³. But drug induced hepatotoxicity is also associated with Anti-Tuberculosis Treatment regimen (ATT)⁴.

The patients suffering from Tuberculosis are unable to complete treatment course due to ATT induced hepatotoxicity. Hence some adjuvant therapy to reduce the ATT induced hepatotoxicity is required.

Ayurveda, a treasure of herbal formulations with proven hepato-protective and antioxidant activity may give solution to this problem. Present paper is aimed to discuss the integrative approach in the management of hepatotoxicity.

Method

Material presented here was obtained through literature searches performed in *Ayurvedic*- classical texts. The information was supplemented by search through Google scholar and data bases like Pubmed, Embase during the

period of Aug 2014 to Dec 2014 by using various combinations of the terms ‘tuberculosis,’ ‘treatment,’ ‘hepatitis,’ ‘liver injury,’ ‘hepatotoxicity,’ ‘adverse events,’ and/or individual names of the anti-TB medications mentioned here. Besides the herbs were searched for hepatoprotective activities with their Latin names viz: *Adhatoda vasica* (Nees), *Azadirachta indica* (A.juss), *Tricosansanthes dioica* (Roxb), *Terminallia chebula* (Retz), *Curcuma longa* (Linn), *Berberis aristata* (DC).

Contemporary Review

Drug induced hepatotoxicity is a potential complication with some medications. More than 1000 drugs ranging from NSAIDs to Valproic acid have been recognized as hepatotoxic drugs and this is a challenging task for medical fraternity. Drug induced hepatotoxicity is accountable for 5% of all hospital admissions, and 50% of all acute liver failures. Thus it is a problem of increasing significance and has been a long-standing concern in the treatment of various diseases including Tuberculosis (TB)⁵.

About one third of the world's population has latent TB and roughly 9 million cases of active TB emerge annually resulting in about 2-3 million deaths¹. WHO report 2013 stated that India had largest number of cases 26% of global total. Besides, a higher risk of hepatotoxicity due to ATT has been reported in Indian patients (up to 11.5%) than western population (up to 4.3%)⁶.

Currently to prevent resistance and achieve successful cure of active Tuberculosis it is recommended to start a chemotherapy containing INH, RMP and PZA with or without Ethambutol for the early 2 months followed by a continuation phase of 4-6 months of INH + RMP as a complete regimen³.

But drug induced hepatotoxicity is identified as a potentially serious adverse effect of INH, RMP and PZA⁴.

The details of the mechanism of toxicity have been explained below.

Isoniazid (INH)

Isoniazid is metabolized mainly in liver, primarily through

acetylation by N-acetyl transferase 2 (NAT-2) and Acetyl-isoniazid is formed which is non-toxic. Acetyl-isoniazid gets hydrolysed to mono-acetyl hydrazine (MAH) and isonicotinic acid (INA). The MAH is further converted to non-toxic diacetyl hydrazine by acetylation. INA gets conjugated with glycine to form isonicotinglycine (INAG) which is further hydrolysed by isoniazid hydrolase to form INA and hepatotoxic hydrazine⁷. The reactive metabolites of MAH are hepatotoxic to tissues through free radical generation⁸. It has been revealed in animal studies that, the free radical scavenger glutathione-related thiols, antioxidant glutathione peroxidase and catalase activities are diminished by isoniazid whereas glutathione reductase activity is increased⁹. In Addition to above said pathology, metabolic idiosyncratic mechanisms seem to be effective. The INH metabolite, acetyl-hydrazine covalently binds to liver macromolecules and causes hepatic necrosis¹⁰. INH inhibits the activity of several cytochromes including P450 2E and 2C enzymes and raises the plasma concentrations of other potentially hepatotoxic drugs¹¹. Hence incidence of hepatotoxicity is more when INH and RMP are used in concomitantly.

Rifampicin (RMP)

Hepatotoxicity produced due to Rifampicin may be due to dose dependent interference with bilirubin uptake and results in subclinical, unconjugated hyper bilirubinemia without hepatocellular damage¹². RMP is a known microsomal enzyme (P-420 2E1) inducer¹³. RMP appears to enhance metabolic hepatocellular idiosyncratic reaction in patients receiving INH, probably by assisting the formation of toxic INH metabolites¹⁴.

Pyrazinamide (PZA)

Pyrazinamide, a nicotinic acid derivative is one more potent hepatotoxic agent of ATT regimen. PZA is de-amidated to pyrazinoic acid in the liver and further metabolized to 5-hydroxy-pyrazinoic acid. During metabolism 5-hydroxy-pyrazinamide may also yield additionally¹⁵. PZA may demonstrate both dose dependent and idiosyncratic hepatotoxicity. PZA exhibits alteration in nicotinamide acetyl dehydrogenase levels in rat liver¹⁶ resulting in

formation of free radical species. As the molecular structures of INH and PZA are similar they might share the common mechanism of injury.

Clinical Characteristics of Isoniazid, Rifampicin, Pyrazinamide Induced Hepato-toxicity

Some individuals may be asymptomatic, whereas others may experience symptomatic hepatotoxicity at varying serum transaminase concentrations. Nausea, vomiting, malaise, fever and abdominal pain, overt jaundice, dark urine, and clay-coloured stools are late signs of clinical worsening. Coagulopathy, hypoalbuminemia, and hypoglycaemia signify life-threatening hepatic dysfunction⁵.

Hepatic Enzyme Measurement

An increase in serum alanine aminotransferase (ALT) previously known as serum glutamic pyruvate transaminase (SGPT), is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST) formerly recognized as serum glutamic oxaloacetic transaminase (SGOT).

Ayurvedic Review

Ayurveda, the age old science has no direct reference of drug induced hepatotoxicity. In Ayurvedic purview toxicity is a condition of '*Vishad*' and the drugs produce '*Vishad*' are *Visha*¹⁷. Hence all those drugs which produce delirious effect on body can be considered as '*Visha*'. The therapeutic chemical drugs which have adverse drug reaction in the form of toxicity may be considered under the concept of '*Abheshaj Dravya*', '*Dooshi Visha*' or '*GaraVisha*'.

'*Abheshajdravya*' are the drugs which show adverse effect and are classified as '*Badhan*' & '*Anubadhan*'. The '*Badhandravya*' shows acute sensitivity reaction whereas '*Anubadhandravya*' produces chronic toxicity¹⁸. The classical text had not explained treatment of '*Abheshajdravya*'.

'*DooshiVisha*' is a poison of any origin and possessing the property to vitiate *Dhatu*. Because of its mild potency,

it is not fatal for an individual. As it is enveloped by the *Kapha*, resides in the body for many years and gets aggravated by cloudy day and exposure to cold and windy atmosphere¹⁹. The ATT drugs do not produce hepatotoxicity under influence of such aggravating factors. Hence although ATT drug induced hepatotoxicity is achronic type of toxicity it cannot be considered under the category of '*Dooshivisha*'.

'*GaraVisha*', one form of *Kritrim Visha*²⁰ are formed by the combination of two or more than two poisonous or non-poisonous drugs²¹. To explain the *GaraVisha*, sages have used two terms '*Virudhaaushdhi bhasmanam*²²' and '*Vividhaushdhihi*²⁰'. The commentator explained term '*Virudhaaushdhi bhasmanam*' as 'the medicine which are having opposite attribute to that of individual's body and exhibits adverse reaction in form of toxicity. This reaction may vary individually. This may be correlated to metabolic idiosyncratic mechanism, one of the pathophysiology explaining hepatotoxicity caused due to ATT drugs. Besides the literary meaning of the term '*Vividhaushdhihi*' is combination of drugs. In ATT regimen four chemical entities are used in combination. The epidemiological survey revealed that although the individual drug of ATT regimen shows hepatotoxicity but in combination they enhance toxic effect. Besides *Yakritdushti* (disorders related to liver) has been quoted as one of the manifestation of '*Garavishajanya vikara*²³' which has been speculated as a major and serious adverse effect due to ATT drugs. Thus ATT drugs may be considered on the boundaries of '*Garavisha*' rather than '*DooshiVisha*' or '*Abheshajdravya*'.

'*Hetuviparitchikitsa*' is a basic line of treatment adopted in Ayurved. Hence the drugs having antitoxic action may be the drug of choice in treatment of ATT induced toxicity. *Yakrit* (Liver) is a *Mulasthana* (Root) of *Raktavahasrotas*²⁴. Also Jaundice (*Kamala*), the late manifestations of ATT drug induced hepatotoxicity is one of the '*Raktapradoshajavyadhi*' (blood disorder)²⁵. Moreover the embryological origin of liver is blood tissue hence the baseline treatment modality of blood disorder may be adopted for liver disorders²⁶.

The critical review of classical text²⁷ revealed that following herbs enlisted in Table No.1 has been quoted for the treatment of *Garavishajanya Vishaktata*.

Table 1: List of Herbs having hepatoprotective activity and used in treatment of *Gara Vishajanya Vishaktata*

Sr.No.	Herbal Drug	Botanical Name
1.	<i>Vasa</i>	<i>Adhatoda vasica</i> Nees
2.	<i>Nimba</i>	<i>Azadirachta indica</i> A.juss
3	<i>Patola</i>	<i>Tricosanthes dioica</i> Roxb
4.	<i>Haritaki</i>	<i>Terminallia chebula</i> Retz
5.	<i>Haridra</i>	<i>Curcuma longa</i> Linn
6	<i>Daruharidra</i>	<i>Berberis aristata</i> DC

All the above said herbs are *Tikta rasatamak* and *Yakritagami* (bitter drugs having action on liver). They are also possessing hepatoprotective activity. Amongst the six *rasa Tikta rasa* (bitter) has been quoted *Vishaghana* (antitoxic) in nature²⁸.

These drugs also have action as *rakta-prasadan* (quality enhancing), *prashaman* (pacifying), *shodhan* (purification) and may prove a good choice of drug in the management of ATT drugs induced hepatotoxicity.

Following lines describe the various clinical and preclinical trials to prove hepatoprotective activity of these herbs.

Vasa (Adhatodavasica Nees)

*Dipankar B., Shrikanta P et al*²⁹ proved significant hepatoprotective effect of aqueous leaf extract of *Adhatodavasica* (AV) at doses of 50–100 mg/kg, on liver damage induced by D-galactosamine in rats. Similar results exhibited by aqueous extract of *Vasa* in paracetamol induced hepatic damage with the reduction in the levels of serum ALP, AST and increased the total protein and albumin/globulin ratio level significantly³⁰. Another in vivo study proved hepatoprotective effect of ethyl acetate extract

of *Adhatoda vasica* against CCl₄ induced liver damage. The assessment parameter was serum ALT, AST, ALP and Bilirubin³¹. Similar findings were revealed in an experiment carried out in adult male Wistar rats and provides conclusive evidence for the hepatoprotective effect of ethanolic extract of *Vasa* against CCl₄ induced hepatotoxicity. The probable mechanism of the hepatoprotective action of AV claimed is its antioxidant effect³².

Nimba (Azadirachta indica A.juss)

*Kale B.P., Kothekar M.A., et al*³³ proved hepatoprotective activity of *Nimba* in an experimental study against hepatotoxicity induced in rats by ATT. Aqueous leaf extract of *Nimba* significantly prevented changes in the serum levels and on histology proving its hepatoprotective activity. In another study an aqueous leaf extract of *Azadirachta indica* in paracetamol induced hepatotoxicity significantly reduced elevated levels of AST, ALT. Also the liver necrosis was found to be reduced macroscopically and histologically³⁴.

The same results were exhibited by fresh juice of tender leaves of *Azadirachta indica*. It induces lipid peroxidation and prevents depletion of sulphhydryl groups in liver cells. Pre-treatment of *Azadirachta indica* stabilized the serum levels of liver enzymes. Histopathological observations of liver tissues corroborated these findings³⁵. Pre-treatment of Aqueous *A. indica* leaf extract showed hepatoprotective effect on the biochemical parameters against NDEA induced toxicity in male mice³⁶.

Patola (Tricosanthes dioica Roxb)

*Ghaisas MM, Tanwar MB et al*³⁷ assessed the potential hepatoprotective effect of *Trichosanthes dioica* Roxb. in ferrous sulphate (FeSO₄) induced hepatotoxicity in rats. It showed significant reduction in AST, ALT, ALP, TB and increase in TP level. The pretreatment with Aqueous and ethanolic extracts of *Patol* showed profound histopathological protection to liver cells concluding the hepatoprotective activity of *Trichosanthes dioica* Roxb.

Haritaki(Terminallia chebula Retz)

95% ethanolic extract of *Terminallia chebulla* prevents the hepatotoxicity caused by the ATT drug in combination in a sub-chronic model. The investigator claimed that the hepatoprotective effect of TC extract could be attributed to its prominent anti-oxidative and membrane stabilizing activities³⁸. Hyun-Sun L., Nam H. W., et al³⁹ proved that treatment and pre-treatment of the hepatocytes with the Aqueous Extract of *Haritaki* significantly reversed the t-BHP-induced cell cytotoxicity and lactate dehydrogenase leakage. In addition, exhibited in vitro ferric-reducing antioxidant activity and 2,2-diphenyl-1-picrylhydrazyl free radical-scavenging activities. Histopathological examination of the rat livers showed that *Haritaki* reduced the incidence of liver lesions, including hepatocyte swelling and neutrophilic infiltration, and repaired necrosis induced by t-BHP. Thus *Haritaki* has potential to prevent hepatic oxidative damage in living systems.

Haridra(Curcuma longa Linn)

In a clinical study hepatoprotective activity of curcumin enriched (25%) *Curcuma longa* and a hydro-ethanolic extract enriched (50%) *Tinospora cordifolia* was assessed in the subjects suffering from active TB. The combination prevented hepatotoxicity significantly and improved the disease outcome as well as patient compliance without any toxicity or side effects⁴⁰. Singh M, Sasi P, et al⁴¹ investigate the role of *Curcumin*, main active phytochemical of *Haridra* on hepatotoxicity by ATT drugs using model of human hepatocellular carcinoma cell line (HepG2). The results suggested that the presence of *curcumin* during treatment of HepG2 cells with ATT drugs lowers the hepatotoxic effect.

Daruharidra(Berberis aristata DC)

An aqueous-methanol extract of *Berberis aristata* fruits showed hepatoprotective effect against paracetamol and CCl₄ induced hepatic damage. Pre-treatment of animals with crude extract reduced the death rate to 10% and

showed reduction in AST & ALT levels. Anwar U., Gilani H. et al⁴² claimed this hepatoprotective action of *Berberis aristata* fruits partly through microsomal drug metabolizing enzymes (MDME) inhibitory action. Potdar D., Hirwani R. et al⁴³ also acknowledged hepatoprotective property of *Daruhridra* in a review article.

Thus all the above said herbal drugs had proved their hepatoprotective activity in various in vivo or vitro or clinical studies.

Few herbal formulations have also proven for their hepatoprotective activity. Some of the studies are mentioned as follows.

An Ayurvedic proprietary medicine Liv-52 has been proved its hepatoprotective activity against ATT induced hepatotoxicity in wistar albino rats⁴⁴.

Gudapippali, *Vasa Guluchyadi Arkom*, *Patolakaturohinyadi Arkom*, *Drakshadi Arkom* and *Madantha* Decoction found to be effective in CCL₄ induced hepatotoxicity in albino rats. Out of these five drugs maximum reduction is speculated by Patolakaturohinyadi Arkom in serum and liver enzyme levels as well as serum bilirubin indicating its superiority over the other drugs⁴⁵.

A preclinical study was undertaken to evaluate the hepatoprotective activity of six commercially available formulations namely Liv 52, Livergen, Livokin, Octogen, Stimuliv and Tefroliv in acute liver toxicity in mice model induced by paracetamol (PCM). The experimental study revealed that the pre-treatment in low doses with liquid formulations of Liv 52 and Livergen reversed the PCM induced liver toxicity whereas at higher doses, all the six herbal formulations conclusively showed marked beneficial effects in the pharmacological, biochemical and histological parameters⁴⁶.

Discussion

The incidence of tuberculosis is higher in Indian population due to various factors like density of population, low socio-

economic status, poor hygienic conditions, malnutrition etc. The effective treatment regimen for Tuberculosis is chemotherapy of drugs viz. Isoniazid, Rifampicin Pyrazinamide, with or without ethambutol. The former three have potent hepatotoxicity.

The pathogenesis of hepatotoxicity is not entirely clear, but INH and RMP induced damage may involve oxidative stress, lipid peroxidation, choline deficiency leading to lowering of phospholipids protein synthesis with alteration in cell wall configuration, reduced glutathione level and activation of CYP2E1. A review of available literature suggests that reduction in lipid peroxide content in tissue and increase in superoxide dismutase, catalase, glutathione, glutathione- transferase and glutathione peroxidase activities should help to maintain liver cell integrity and control the increase in level of liver enzymes. Thus oxidative stress and idiosyncratic reactions play major role as a causative factor of hepatotoxicity due to ATT drugs⁵.

As discussed above the ATT drugs are potent hepatotoxic but the manifestation of toxicity are not seen similar in all the patients receiving the drugs. This may be due to the idiosyncratic reaction of individual owing to individuals *Prakriti* (Basic body constitution). In *Ayurvedic* purview, the chemical drugs causing hepatotoxicity used for treatment of Tuberculosis may be considered under the realm of '*Abheshjadravya*', '*Dooshivisha*' and '*Garavisha*'. But they are best correlated as *Gara Visha* one form of *kritrim Visha* and the drug induced hepatotoxicity can be considered under as *Garavishajanya Vishaktata*. The herbs mentioned for the treatment of *Garavishajanya Vishaktata*, has been reviewed for their hepatoprotective activity and revealed promising results in preclinical and clinical experiment. Thus the drugs mentioned for the ailments of *Gara Vishalike Vasa*, *Patola*, *Nimba*, *Haritaki*. *Haridra* and *Daruharidra* may be used successively to reduce hepatotoxicity caused by ATT drugs and may provide support to the treatment regimen for complete cure of Tuberculosis.

Conclusion

Anti-tubercular drug induced toxicity can be considered under the boundaries of '*Garavisha*'. The herbs prescribed for the treatment of *Garavisha* having *Tikta rasa*, action on *Raktavahasrotas* along with *Yakritagamitva* may be used as hepatoprotective in the management of hepatotoxicity caused due to ATT drugs. Preclinical and clinical studies are required to be conducted to prove this hypothesis.

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