Herbal Treatment of Tuberculosis

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Muhammad Ifham Naeem[1]*, Muhammad Younus[2], Aisha Ambreen[3], Qamar un Nisa[4], Tayyaba Akhtar[5], Muhammad Arfan Zaman[6] and Tayyaba Ameer[1]

ABSTRACT

TB is a major threat to public health in the present era. TB as a problem has now become so severe for public health that it has now become a topic of constant debate on international health platforms. Now international health-related organizations have started emphasizing the importance of proper treatment for TB to control and eradicate TB. These programs started getting special attention after the emergence of drug resistance in etiologic agents of TB along with the revelation of the fact the rigorous administration routines of anti-TB drugs are leading to increased cases of hepatotoxicity in patients. This happens due to long dosing regimens of the TB drugs along with high doses being administered to counter drug resistance and eradicate the disease completely.

All these issues call for a new perspective on TB medication. Such an alternative is a medication manufactured from herbal extracts. This option kills two birds with one stone. It battles antibiotic resistance while minimizing the chances of liver damage and hepato-toxicity. The herbal extracts have a low cost of manufacturing and do not contain lethal amounts of toxins rendering them safe for consumption even in large amounts. Such useful characteristics of herbal medicine extracts necessitate thorough research to identify useful plants and the parts required to manufacture effective remedies.

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[1]KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[2]Department of Pathobiology, KBCMA College of Veterinary and Animal Sciences, Narowal, Sub-campus UVAS Lahore, Pakistan.
[3]Department of Biochemistry, Faisalabad Medical University, Faisalabad
[4]Department of Pathology, University of Veterinary and Animal Sciences-Lahore.
[5]Department of Epidemiology & Public Health, University of Veterinary and Animal Sciences-Lahore.
[6]Department of Pathobiology, College of Veterinary and Animal Sciences, Jhang, Sub-campus UVAS Lahore, Pakistan.
***Corresponding author:** afhamnaim4@gmail.com

1. INTRODUCTION

TB or Tuberculosis is one of the most irresistible seasoned diseases to befall mankind (Sharma and Mohan 2013). It is a disease spreading from poor hygiene practices that affects the pulmonary system of the affected individual (Pereira et al. 2005). TB affects a devastating number of almost 8 million individuals annually. This *Mycobacterium tuberculosis* infection then leads to the demise of around 2-3 million patient's unfortunate patients (Dimayuga and Garcia 1991). The old sacred Indian text Vedas referred to TB as wasting illness or Yakshma. Robert Koch was the first scientist who discovered and announced the presence of tubercle bacillus during the monthly evening meeting of the Berlin Physiological Society on the 24th of March 1882. This date of March 24th was later selected to be the 'World TB Day' for crediting its revelation. Every year this day is celebrated to raise awareness among people regarding the control of TB (Sharma and Mohan 2013).

2. NEED FOR USE OF HERBAL MEDICINE

A study revealed that about 5 to 20%of people, undertaking the anti-TB medication were reported to have liver problems. These hepatic complications become severe due to the regimes of drug combinations (Arbex et al. 2010). INH, PZA, ethionamide (EMB), para-aminosalicylic acid (PAS) and RIF were discovered to be the cause of hepatic issues (Saukkonen et al. 2006). Hepatotoxicity is a common occurrence post-use of anti-TB drugs worldwide (Sharma et al. 2004). Clinically affected people display symptoms like abdominal pain, nausea, jaundice and vomiting. The laboratory testing of blood may also reveal increased levels of hepatic transaminases and bilirubin (Sharma and Sharma 2015). The anti-TB drug-related hepatotoxicity is a major reason for increased morbidity and mortality in TB patients undergoing treatment. Under these circumstances, the mortality rate jumps up to 6%- 12% after liver disease onset in TB patients who continue the use of hepatotoxic anti-TB drugs (Ali et al. 2013). The liver is a crucial organ that modulates several physiological mechanisms. It helps in the synthesis of several important molecules such as cholesterol, albumin, bile acid and fibrinogen. The liver is a major producer of proficient foreign molecules transforming enzymes. These enzymes in turn enable the liver to detoxify and metabolize several types of autochthonous (steroids, fatty acids etc.) and heterochthonous chemicals (drugs, insecticides, etc.) (Bedi et al. 2016).

Detoxification of drugs in the body by administration of Cytochrome P450 happens in three phases. These phases include transportation into bile, conjugation and transformation. Any anomaly in either of these phases can lead to hepatotoxicity. The covalent binding of the metabolite or drugs as a whole with host proteins produces oxidative stress that is the leading cause of liver injury (Saukkonen et al. 2006; Ramappa and Aithal 2013). Stress by oxidative agents can lead to damaged intracellular macromolecules. The macromolecules that usually face damage due to oxidative stress include DNA, RNA, lipids, glutathione, ATP and proteins (Bhattacharyya et al. 2014). Liver toxins also lead to the induction of an inflammatory response in the liver. Inflammation of the liver in turn causes activation of STAT3, MAPKs and NFkB signaling pathways (Ambade and Mandrekar 2012). The metabolism of anti-TB drugs leads to the production of several intermediate products that cause liver damage. Such an example is the metabolism of INH which produces acetyl diazine. This is then further processed into acetyl onium ion, ketene and acetyl radical. The conversion enzyme N-acetyltransferase 2 (NAT2) changes acetyl hydrazine to diacetyl hydrazine (DAH) through acetylation. Diacetyl hydrazine is non non-toxic product for cells however, in the presence of INH the process of acetylation is slowed down. A slowed-down acetylation results in an increased amount of non-acetylated hydrazines. These intermediate products can be toxic to the liver and cause hepatic injury (Scales and Timbrell 1982; Ramappa and Aithal 2013). Just like INH, PZA also induces oxidative stress and liver toxicity through the production of 5-hydroxypyrazinoic acid. PZA is converted to

pyrazinoic acid by the activation of the amidase enzyme. The pyrazinoic acid product is then hydroxylated to form 5-hydroxy pyrazinoic acid through a xanthine oxidase reaction ultimately leading to hepatic distress (Shih et al. 2013). Similarly, RIF can also cause toxicity when administered in combination with other drugs. RIF induces enzymatic pathways like (CYP3A4) Cytochrome P450 through (PXR) or hepatocyte Xeno Sensing Pregnane X Receptor. The time duration of the anti-TB drug combination regime is a crucial factor in determining the amount of RIF that could increase the metabolism of INH in turn leading to the formation of toxic metabolic intermediate products. The induction of isoniazid hydrolases in this process leads to increased hydrazine production. Increased hydrazine consequently alters the expression of proteins controlling the process of lipid metabolism (Guldberg Klenø et al. 2004). Prolonged exposure to RIF can produce hepatic distress through altered membrane permeability. This situation leads to considerably reduced activity of glucose-6-phosphate. Reduction in the activity of glucose-6-phosphate is one of the causes of the heightened lipid peroxidation in the liver (Koster and Slee 1980; Saraswathy and Devi 2001; Santhosh et al. 2006; Singh et al. 2016). Hence it can be established collectively that antiTB drugs lead to the production of toxic intermediate metabolites, free radicals and reactive oxygen species (ROS). These agents are the main sources of hepatic injuries. The drugs of anti-TB nature also interfere with normal lipid deposition. The interference produced by these drugs leads to activating CYP2E1, LDL uptake and fatty acid accumulation ultimately disturbing the lipid deposition. (Anundi et al. 1993; Upadhyay et al. 2007; Singh et al. 2016).

3. PREVIOUS ATTEMPTS AT TREATMENT

TB is an exceptionally contagious ailment and around 40% of people from India carry TB germs in their bodies making it the largest reservoir country of the disease (Agarwal 2004). The WHO indicated in 1998 that tuberculosis (TB) is a contagious disease caused by the bacillus *M. tuberculosis* (WHO 1998). Lungs are predominantly influenced by *M. tuberculosis*, this is the main reason leading to lung tuberculosis also known as pulmonary tuberculosis, after infection (Gangadharam 1993). In other instances, various parts and portions of the body can be found affected by TB likewise resulting in extra-pulmonary form of tuberculosis (Sharma and Mohan 2004). TB spreads more effectively in jam-packed environments where there is a lack of healthy practices, hygienic sustenance and poverty (Pereira et al. 2005). The primary source for the transmission of TB is likely the aerosol route through droplets from coughing or sneezing of a TB-affected person resulting in the release of Tubercle bacilli in the surrounding environment (Narwadiya 2011). Some typical symptoms of TB include chest pain, hemoptysis, coughing, fatigue, reduction in weight, and fever (Stanhope and Lancaster 1996). Even though high rates of curability can be achieved through treatment against TB by using antibiotics it is still spreading rapidly (Loddenkemper and Hauer 2010; Sloan et al. 2013). The marvelous weapons of medicine are antibiotics, starting with streptomycin (Schatz et al. 1994) and penicillin (Kardos and Demain 2011), which changed the system of medication after their discovery during the 1940s. These antibiotics provided mankind with suitable remedies for the most commonly occurring diseases of that time. However, hindrance in the advancement of antibiotics has confined the helpful life expectancy of antitoxins. This resulted in the necessity of a constant struggle to present new mixes (Spellberg and Shlaes 2014).

4. TREATMENT OF ZOONOTIC TUBERCULOSIS

The main threat prompted by Tuberculosis as a disease is its potential to rapidly burgeon into a significantly epidemic situation due to its exponentially high rate of transmission. This leads to the classification of TB as a reportable contagious disease. The characteristic variation in clinical appearance and status of TB

requires a thorough understanding of the underlying mechanisms related to the activation of diseases. This knowledge helps in the accurate diagnosis of TB along with helping us to identify the need for further tests (Lee 2018). The severity of tuberculosis is often underscored due to the appearance of secondary lesions. A few of these could even prove to be fatal. The potentially life-threatening situation arising from these lesions can lead to prolonged courses of antibiotic administration. Under certain circumstances of severe nature surgical intervention may also be needed. The severity of the impact made by TB on individual affected is thus linked in a sophisticated manner to the condition of secondary lesions. In an extended attempt to reduce the spread of TB, the main emphasis is placed on adopting a preventive approach. The preventive approach should encompass strict hygiene practices, vaccination of livestock should be enforced, awareness should be raised among the public and the consumption of unpasteurized dairy products should be discouraged (Abe et al. 2003).

Djibouti is rich with medicinal herbs boasting an extraordinary reservoir of biodiversity in terms of plant population. Djibouti houses a broad range of plant species. It holds promise for a stockpile of medically applicable herbs as an alternative herbal medicine. Researchers and scientists are working hard to come up with an extensive exploratory explanation for the options related to the use of these botanical resources. They are also trying to uncover the potential of Djibouti for finding the herbal treatments of diverse diseases and issues (Abdoul-latif et al. 2020; Ainane et al. 2020; Abdoul-Latif et al. 2022A; Abdoul-Latif et al. 2022B; Mohamed Abdoul-Latif et al. 2022A). These exploratory efforts have resulted in the discovery of several plant-based bioreactors as a potential avenue for the production of recombinant therapeutic agents of a protein nature targeted at animal health improvement. This innovative strategy emphasizes the collection of traditional knowledge and bleeding-edge biotechnology to resolve current challenges (Ainane et al. 2021; Mohamed Abdoul-Latif et al. 2022B; Mohamed Abdoul-Latif et al. 2023). The increasing interest in herbal medicine in the realm of veterinary medicinal practice is driven by several aspects. One important driving force out of these factors is the emergence of the idea among people that medicinal herbs have better efficacy and safety in contrast to chemical compounds. This strong belief exists among both practitioners and the general people alike. The existence of this idea led to the growing use of herbal medicine in veterinary practice. The major shift towards herbal remedies reflects an evolution of the veterinary medicine paradigm, aligning this one with holistic aspects and giving it a deeper connection with mother nature (Shin and Park 2018).

At the core of the epidemiological studies related to bovine tuberculosis, lies an enigmatic confusion as it shows disparity in prevalence levels. The disparity becomes evident when contrasting prevalence levels appear at the individual level which is low and an increased level of TB prevalence is seen within herds. This surprising disparity between individual and communal dynamics of TB provides it with a unique disease profile. There are also numerous instances of TB being reported at below-threshold levels across several herds. This intriguing pattern of TB bases itself upon the complex infection dynamics and management practices related to the control of disease within infected people. The nature of these complex dynamics is based upon the complexity integrated into comprehending the spread of bovine tuberculosis. It is further supported by the crucial need for multi-dimensional tactics to limit the spread of TB and for its prevention (Ntampaka et al. 2022).

In the context of the herbal medicinal herbs Djibouti has prime importance for holding most of the medicinal herb species. The effects of bovine tuberculosis on both public health and the productivity of livestock remain somewhat contained in such regions because of these effective plants. The limited number of virulent TB strains that can pose a direct threat to human health via raw milk consumption, is one of the mitigating factors controlling the spread of bovine TB. On the other hand, the existence of even a small number of instances provides the basis for the latent potential of TB transmission and demands

vigilance for its control. As farming methods intensify for better production with the simultaneous evolution of environmental and anthropogenic factors, the latent risks related to bovine tuberculosis's emergence into human populations can be expected. The complex relationship between TB and the wide-spectrum biodiversity of Djibouti presents a multi-dimensional mix of issues and opportunities. The potential of tuberculosis to transform into a proportionally significant epidemic necessitates vigilance of the utmost level. Early detection of disease and the implication of stringent preventive measures are the first steps for its control. Simultaneously Djibouti's abundant plant species should be explored to comprehend how these can offer novel therapeutic remedies crucial to battle TB. Formation of such remedies requires a homogenous mixture of modern science and traditional wisdom. The journey of Djibouti as a remedy calls for collaborative efforts between different domains of knowledge while transcending boundaries to protect the well-being of both animals and humans (Abdoul-Latif et al. 2023; Beyene et al. 2023; Mohamed Abdoul-Latif et al. 2023).

5. MODERN ATTEMPTS FOR TREATMENT OF TB

The latest and most advanced treatment technique for curing TB is dependent on drugs like rifampicin, isoniazid, pyrazinamide and ethambutol. These techniques and the drugs they depend upon are unable to achieve the desired effectiveness (Brigden et al. 2014). Additionally, these drugs are very expensive. Another serious downside of using these drugs is the life-altering side effects that are produced after their usage (Mohan and Sharma 2004; Zazueta-Beltran et al. 2011; Bhatcha 2013). Even if we criminally ignore all those serious side effects the rise of drug-resistant (Gupta et al. 2010; Zazueta-Beltran et al. 2011) and TB etiologic agents, along with the development of geographic-dependent strains (Firdessa et al. 2013) adds fuel to the already fiery situation of TB as an emerging threat in under-development countries of Africa that are already burdened heavy loads of TB. Such a situation calls for a mandatory search to develop new treatment regimens targeting medicinal plants. Hence encouraging the formation of a herbal product that can counter TB while minimizing the chances of developing further antimicrobial resistance (Kloos 1976; Kloos et al. 1978; Hostettmann et al. 2000; Askun et al. 2013; Bhatcha 2013; Andualem et al. 2014).

6. USE OF PLANT ADJUNCTS

WHO has recommended 6 to 9 months of DOTs or Directly Observed Therapy Short as a treatment course for curing TB. In many instances, the drugs used against *M. tuberculosis* infection may produce side effects such as hepatic damage even with the regimen of DOTs combination. The main reason for the liver damage induced by anti-TB is the distinct reaction of metabolism for dealing with these drugs (Rivers and Mancera 2008; Sonika and Kar 2012). The latest approach being followed, to reduce the thereafter side effects and up-surged efficacy of medicinal agents is the basic controlled intake planning. In combination or standalone, the herbs and medicinal plants are effective in reducing the adverse effects of drugs to a minimum. The ethno-medicinal utilization of medicinal herbs against hepatic disease has been documented well in the past. Though along with documentation awareness regarding their uses is also important for effectively treating the disease (Amadi and Orisakwe 2018). Plants and medicinal herbs are major reservoirs of several types of secondary metabolites with broad-spectrum effectiveness. This property enables these plants to play an important role towards the revelation of novel drug moiety against target diseases (Cragg and Newman 2013). The liver protection activities of several herbs against the liver damage induced by anti-TB drugs have been studied in various types of animal models.

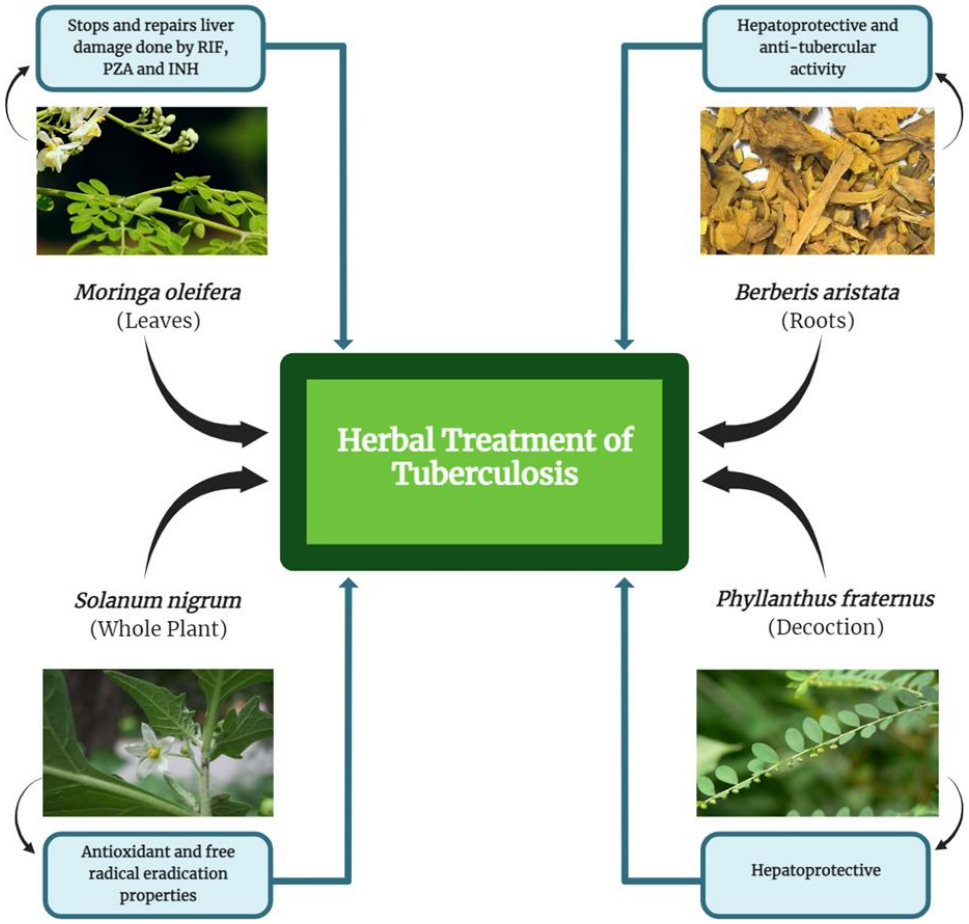

Fig. 1: Different parts of various plants used in the treatment of Tuberculosis. RIF(Rifampin); PZA(Pyrazinamide); INH(Isoniazid).

A study by (Sharma et al. 2004) was based on testing the impact of herbal and anti-TB drug combinations on the livers of the patients ingesting the medicine. Patients were divided into three groups and were studied for 12 weeks. The first group of patients was the one receiving capsules of Aloe vera extracts from the whole plant, whole plant *Solanum nigrum* and roots of *Berberis aristata*. The patients in the second and third groups were given a decoction of *Phyllanthus fraternus* and placebo starch capsules in the same order. At the end of the trial, the activity of liver enzymes and their serum levels were within the normal range in the first and second groups of patients. On the other hand, the third group was found to have a rise in serum levels of AST and ALT. Both the enzymes AST and ALT were used as marker enzymes to identify hepatotoxicity in that study (Sharma et al. 2004). An active source of phytochemicals with both hepatoprotective and antitubercular properties is *B. aristata* (Potdar et al. 2012; Unkeshwar et al. 2013; Mahapatra et al. 2014). Similarly, *S. nigrum* is a plant with potent antioxidant properties that can help it regulate the function of detoxification enzymes involved in the removal of toxic chemicals. It also exhibits free radical eradication characteristics (Lin et al. 2008). *Phyllanthus fraternu* also possesses hepatoprotective properties just like *S. nigrum* (Bera et al. 2011). All these plant extracts act through various mechanisms to produce desired effects (Fig. 2).

Another study by (Debnath et al. 2012) provided information regarding the use of adjunct Ayurvedic therapy with Ashwagandha to manage the pulmonary tuberculosis situation in a patient already ingesting anti-TB drugs. This study claimed that the use of Ashwagandha led to the modulation of the immune system, restoring SGPT and SGOT to their normal levels in the body, while increasing the

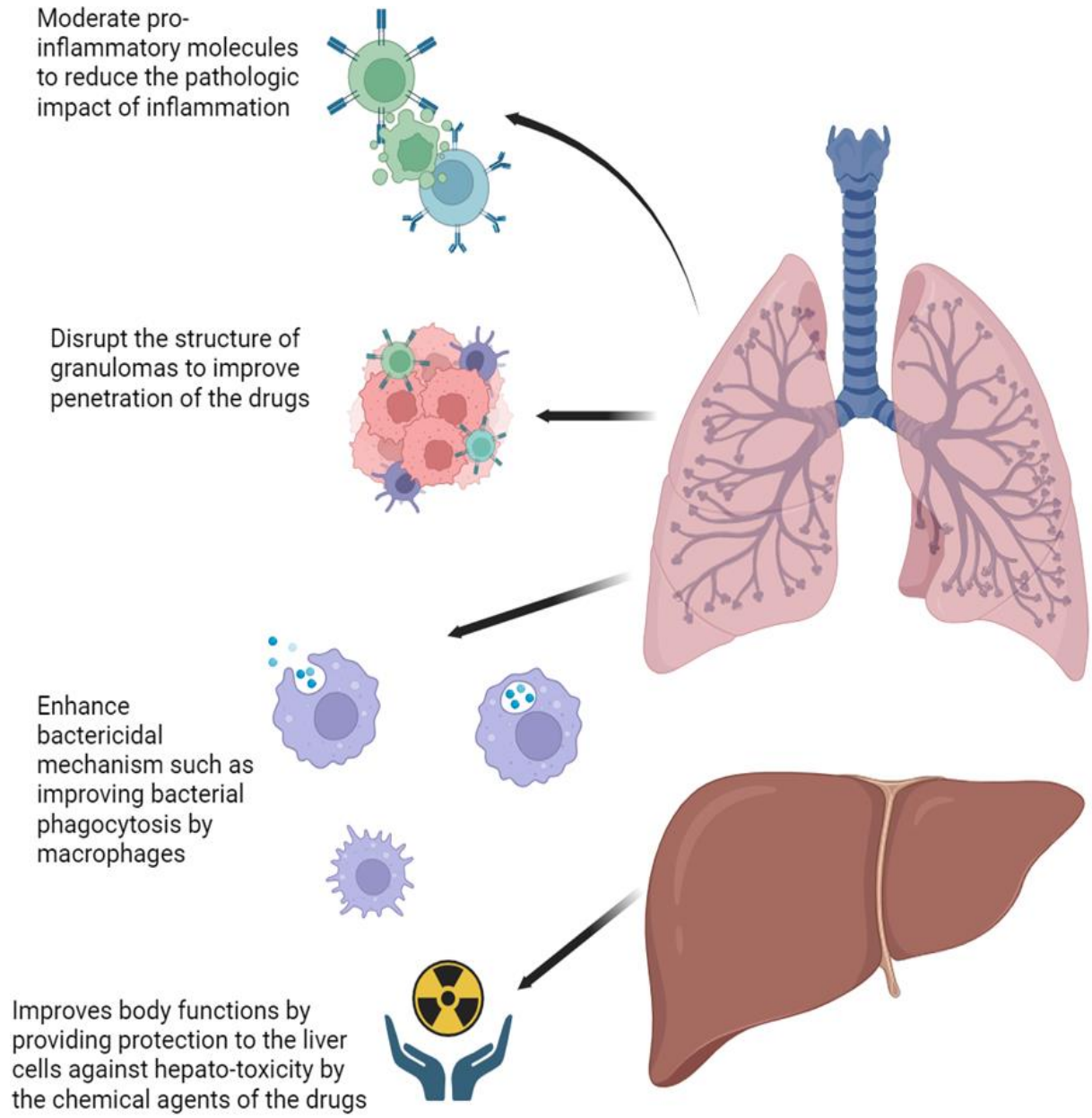

Fig. 2: Different modes of action adopted by anti-TB medicinal herbs to counter the infection and work synergistically with anti-TB drugs.

bioavailability of INH and PYZ at the same time and all this happened within 28 days of treatment against TB. Several in-vitro studies were conducted on animal models using medicinal herbs such as *Ficus religiosa, M. oleifera, Lawsonia inermis, T. chebula, W. somnifera, Tinospora cordifolia, C. auriculata* etc. also support the beneficial effects of these herbs in reduction of liver damage caused by anti-TB drugs. The combined regimen of Ayurvedic and Anti TB drugs can ensure an increase in the chances of survival for patients with pulmonary TB. Various clinical studies have revealed that the patients who were only receiving TB drugs for treatment had a cure and death rate of 11.42 % and 40.9 % respectively. On the other hand, when the patients were given a combined mix of TB drugs and

Table 1: Herbal treatment options for Tuberculosis.

No.	Plant	Part used	Effect	References
1.	*M. oleifera*	Leaf	Stops and repairs liver damage done by RIF, PZA and INH	(Pari and Kumar 2002)
2.	*B. aristata*	Roots	Hepatoprotective and anti-tubercular activity	(Potdar et al. 2012; Unkeshwar et al. 2013; Mahapatra et al. 2014)
3.	*S. nigrum*	Whole plant	Antioxidant and free radical eradication properties	(Lin et al. 2008)
4.	*P. fraternus*	Decoction	Hepatoprotective	(Bera et al. 2011)

Ayurvedic drugs the respective cure and death rates improved to 41.3% and 3.8% (Debnath et al. 2012). A smaller number of systematic studies also supported the effective use of Ayurveda drugs for managing pulmonary tuberculosis disease (Samal 2015). The plant-based preparations can effectively prevent hepatotoxicity and increase the viability of treatment outcomes (Table 1). Additionally, the use of these herbal drugs is free from of any toxicity or side effects that usually accompany the anti-TB drugs (Adhvaryu et al. 2008).

8. CONCLUSION

The main agenda of today's TB researchers is to provide mankind with a fulfilling remedy that can eradicate the disease in the patient while keeping the body of the host safe from the adverse effects of the drugs. The two main aspects of introducing plant-based medicine to treat TB are the use of plant extracts and the challenges faced in applying these remedies. The methodology of using herbal medicine for tuberculosis is being researched thoroughly across the world.

Herbal medicine has been explored as a potential treatment for tuberculosis due to the need for alternative treatment approaches. Several studies have investigated the use of plant adjuncts for the treatment of tuberculosis. Many challenges being faced in implementing herbal treatments are being resolved and new opportunities are being created in the herbal treatment section of the battle against TB. Challenges in the herbal treatment of tuberculosis include the need for further research and clinical validation. Opportunities exist for the development of new herbal-based therapies for tuberculosis treatment.

The leaf of *Moringa oleifera* is a major source of phytochemicals including terpenoids, flavonoids, saponins, alkaloids, carbohydrates, tannins, and glycosides. A study on these leaves reported that oral intake of *M. oleifera* leaf extracts has wondrous effects as it repairs normal liver activity in rats countering the hepatic damage done by RIF, PZA and INH (Fig. 1). These leaf extracts also appear to enhance the recovery of the liver from hepatic damage and restore the functioning of enzymes to normal including normality of factors like AST, lipid peroxidation, ALS, bilirubin and alkaline phosphatase in blood serum (Pari and Kumar 2002). The root extracts of *Cassia auriculata* have a significant impact in lowering the above-normal serum levels of ALT, AST, ALP, cholesterol, protein and total bilirubin found in the blood as a side effect of using anti-TB drugs that lead to hepatotoxicity. These root extracts also maintain the normal levels of the marker of oxidative stress; Malondialdehyde (MDA) and enzymatic antioxidants (Jaydeokar et al. 2014). One of the most highly valued medicinal herbs in Ayurvedic pharmacopoeia is *Terminalia chebula*. It has antioxidant properties along with activities of cell membrane stabilization. The fruits of this plant can prevent hepatotoxicity induced by the intake of anti-TB drug combinations (Tasduq et al. 2006). Plant-based formulations made of *T. chebula* also tend to be hepatoprotective. A study by Sankar et al. (Sankar et al. 2015) revealed that the multi-herbal formulation comprised of *Phyllanthus amarus, Tephrosia purpurea, Cycas circinalis, Pinius succinifera, Curcuma longa, Eclipta alba, Pistacia lentiscus, Orchis mascula, Withania somnifera* and *Picrrohiza kurooa* show supreme effectiveness against the oxidative injuries caused to the liver by INH and RIF in rats. The combination regime of medicinal plants

and anti-TB drugs for enhancing the treatment efficacy with minimal side effects also got supportive results from several clinical trials undertaken in the past.

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