

Plant-derived Molecules for the Treatment of Tuberculosis: A Review

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Abstract

Synthetic anti-TB drugs are being used to treat tuberculosis (TB) as they are effective, however, they are accompanied by many side effects. The disease has remained largely uncured till date. The use of the plant extracts or phytochemicals along with the anti-TB drugs is a very attractive strategy to make the treatment more effective as phytochemicals have no side-effects, are much less toxic than synthetic anti-TB drugs, are safe to use and most importantly, do not produce resistant strains as opposed to synthetic anti-TB drugs. Approximately 420,000 plant species have been identified globally and among them only a few have been explored for their therapeutic potential. Traditional medicine in different parts of the world has employed crude extracts of several plant species to cure tuberculosis. Several anti-TB phytochemicals have been found in the plants that are identified to have therapeutic qualities. These phytochemicals are majorly glycosides, flavonoids, triterpenes, phenolic compounds, alkaloids, diterpenoid, lipids, tannins, sterols etc. They are either antimycobacterial or act synergistically with anti-TB drugs and reduce their adverse effects. Phytochemicals ameliorate the symptoms either by reducing the oxidative stress in the afflicted tissues or by regulating the inflammatory response. Hence, plant derived molecules have great potential to become a part of the alternative treatment strategy for TB in the future.

Keywords: Tuberculosis, plant-derived molecules, antioxidant, anti-mycobacterial, oxidative stress.

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (M.tb) which affects primarily the lungs in humans. It is widespread and is a serious public health issue that needs to be addressed quickly and effectively. The M.tb lineages are spread worldwide with few having global distribution while few remaining restricted to certain regions. The restricted presence of some strains, in specific regions, had been explained by theory of 'local adaptation' in the past, whose latest evidence has been provided by Liu et al. ⁽¹⁾. Wherein they did genome sequencing of hundreds of M.tb strains and confirmed the 'local adaptation' theory in Tibetan population. The seriousness of the disease may be understood by the fact that in the year 2018, around 10 million people had developed TB and 1.5 million had died from it and by 2020, an estimated 1.7 billion people were infected with M.tb. Among the people who get infected with Human Immunodeficiency Virus (HIV), TB is the leading cause of death. Approximately half of the TB patients have been reported from eight countries viz. Bangladesh, China, India, Indonesia, Nigeria, Pakistan, Philippines and South Africa and according to latest WHO update, the success rate of treating multi-drug resistant-TB (MDR-TB) is fifty-six percent ⁽²⁾.

Various synthetic drugs have been produced to treat TB. WHO has classified anti-TB

drugs into five classes; first-line anti-TB drugs (for drug-susceptible TB) which include rifampicin, isoniazid, pyrazinamide, and ethambutol; second-line anti-TB drugs which include amikacin, capreomycin, kanamycin, and streptomycin; the third-line anti-TB drugs which include fluoroquinolones; the fourth class anti-TB drugs which include cycloserine, ethionamide, para-aminosalicylic acid, prothionamide, terizidone, and thioacetazone and fifth-class anti-TB drugs (drugs with unclear efficacy) which include amoxicillin/clavulanate, clarithromycin, clofazimine, imipenem, and linezolid ⁽³⁾. The M.tb strains that are resistant to at least isoniazid and rifampin (first-line anti-TB drugs) are known as multidrug resistant (MDR) and cause MDR-TB ⁽⁴⁾ whereas the M.tb strains that are resistant to isoniazid, rifampin, fluoroquinolones and at least one of the three injectable second-line anti-TB drugs are known as extensively drug resistant (XDR) and cause XDR-TB ⁽⁵⁾. Centers for Disease Control and Prevention (CDC) recommends a 6- to 9-month treatment schedule for TB. The U.S. Food and Drug Administration (FDA) has approved ten drugs for treating TB, out of which four drugs viz. isoniazid (INH), rifampin (RIF), ethambutol (EMB) and pyrazinamide (PZA), form the core of treatment regimen ⁽⁶⁾.

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while National Health Service, United Kingdom recommends INH and RIF for six months and EMB and PZA for first two months of the treatment regimen⁽⁷⁾.

The synthetic drugs used for treating TB cause varied side effects. Hepatotoxicity, nephrotoxicity, ocular toxicity, skin rashes, fever, psychotic alterations are just a few of the adverse effects^(8,9,10). The side effects are manifested in the form of symptoms such as gastrointestinal disturbances, arthralgia, hepatitis, psychiatric disorder, hypothyroidism, peripheral neuropathy, dermatological effects, epileptic seizures, ototoxicity etc.^(11,12). Although, EMB has fewer side effects than thioacetazone but it does show some side effects and the most serious of them is retrobulbar neuritis which is manifested as loss of visual acuity and color vision⁽¹¹⁾. After many trials and testing over the years, WHO now recommends the use of a fixed dose of Myrin®-p Forte- (a combination drug) for treating TB, which includes rifampicin (13.5 mg/kg), isoniazid (6.75 mg/kg), pyrazinamide (36 mg/kg), and ethambutol (24.8 mg/kg) viz. RIPE – for the intensive phase (2 months), followed by continuous rifampicin and

isoniazid administration for four-six months. However, these drugs cause hepatic injuries which are mainly caused due to reactive oxygen species (ROS)-mediated oxidative damage⁽¹³⁾. The current practice of treatment of TB includes a combination of different drugs for a duration of six months for drug-susceptible TB, for 9-20 months for MDR-TB while the duration of treatment can be longer for XDR-TB. The duration can also be longer when the patient is not responding satisfactorily⁽¹⁴⁾. The higher the age of the patients, higher is the risk of severe symptoms of TB. Thus, it is a fact that synthetic anti-TB drugs are accompanied by various kinds of side effects, some of which may have serious implications or may even prove fatal. Some of the common anti-TB drugs, their side-effects and symptoms have been summarized in table 1. The patients suffering from Multi Drug Resistant Tuberculosis (MDR-TB) are advised different treatment regimens than patients with drug-susceptible TB. As a result, the former experience many side effects which are greater in intensity. The patients may experience one or more side effects depending on the dosage of anti-TB drugs⁽¹²⁾.

Table 1. Commonly used Anti-TB drugs and their side-effects

S. No.	Anti-TB drugs	Side-effects	Clinical symptoms	References
1	Rifampicin (RIF)	Hepatotoxicity-hyperbilirubinemia; elevates levels of enzymes like alkaline phosphatase (ALP), serum glutamic oxaloacetic transaminase (SGOT/AST), serum glutamic pyruvic transaminase (SGPT/ALT); allergic reactions	Jaundice, nausea, vomiting, abdominal pain; allergic reactions include fever, rashes, flu-like symptoms, eosinophilia; sometimes haemolytic anemia, hemoglobinuria, and kidney damage	(11)
2	Isoniazid (INH)	Hepatotoxicity; neurologic adverse reactions	Gastrointestinal symptoms; dermatological manifestations; neuropsychiatric adverse effects like peripheral neuropathy, ataxia and paresthesia	(11)
3	Pyrazinamide (PZA)	Hepatotoxicity	Gastrointestinal intolerance; gouty arthritis; non-gouty polyarthralgia	(12, 11)
4	Ethambutol (EMB)	Hepatotoxicity; ocular toxicity; hypothyroidism	Gastrointestinal disturbance, psychosis, hypothyroidism	(11, 12)
5	Streptomycin (SM)	Otovestibular toxicity; nephrotoxicity	Permanent deafness,	(11)
6	Kanamycin (KAN)	Ototoxicity	Hearing loss	(15)
7	Capreomycin	Nephrotoxicity, ototoxicity, electrolyte disturbance	Loss of balance; hearing loss	(16)
8	Amikacin	Renal dysfunction	Skin rash	(3)
9	Fluoroquinolones (FQN)	Less hepatotoxicity than first-line anti-TB drugs	Gastrointestinal problem; allergic reaction; psychosis	(12, 17)

Hepatotoxicity is the predominant side effect of synthetic anti-TB drugs. These drugs induce hepatotoxicity in 5-28 percent of individuals, and they are one of the common causes of hepatotoxicity worldwide. The common clinical symptoms of hepatotoxicity include jaundice, nausea, vomiting and abdominal pain. It is also accompanied by higher levels of bilirubin and increased activity of hepatic transaminases. Due to these symptoms, many times, therapeutic doses are frequently reduced, which is one of the leading causes of treatment failure. These symptoms are also the biggest reason for discontinuation of the therapy which might be a cause for development of resistant forms of *M.tb* ⁽¹⁴⁾. Experts no longer recommend capreomycin, kanamycin, amoxicillin/clavulanate (when administered without a carbapenem), azithromycin, or clarithromycin for treating MDR-TB due to serious adverse effects documented after using these anti-TB medications over the years ⁽¹⁶⁾. However, other synthetic anti-TB drugs are still largely being used to treat TB as they are effective despite of their adverse side effects and there is no concrete alternative strategy to treat TB more effectively. In spite of several drugs available for treating TB, the disease remains largely uncured. Further, there is only one licensed vaccine *viz.* Bacille Calmette-Guerin (BCG) that can prevent the development of severe TB in children. There is no such vaccine for adults yet ⁽¹⁸⁾.

Exploring Plants for Molecules with Anti-TB Properties

Synthetic anti-TB drugs have numerous side-effects, are less efficient and also cause drug resistance in mycobacteria. Hence, there is much need to look for alternative strategies to treat TB. The newer strategies must emphasize improving TB treatment methods, reducing side effects, and maintaining safety of usage. A very good alternative strategy would be to use plant products along with

synthetic anti-TB drugs. Plant-derived molecules show fewer side effects, have less toxicity, are less likely to develop resistance, and have better efficacy ⁽¹⁹⁾, hence could become a good source of alternative medicine for TB.

Plant-derived molecules as potential anti-TB drugs

Various studies have shown that the side-effects of the anti-TB drugs can be ameliorated by using natural products obtained from the plants. The plant-based products are diverse and can provide effective plant molecules or phytochemicals for treating TB. Phytochemicals are secondary metabolites of plants and unlike primary metabolites, which are essential for plant growth and development, the secondary metabolites are not directly involved in growth, reproduction or development of plants but they influence plant's survival and defense system ⁽²⁰⁾. Plants that are effective against TB are rich sources of alkaloids, flavonoids, glycosides, diterpenoid, triterpenes, lipids, phenolic compounds, tannins, sterols etc., all of which have hepatoprotective function ⁽²¹⁾. For example, leaf extracts of *Moringa oleifera* contain phytochemicals like alkaloids, flavonoids, carbohydrates, glycosides, saponins, tannins and terpenoids. They repair liver damage caused due to INH, PZA, and RIF when given orally by restoring normal levels of hepatic enzymes, serum bilirubin, and lipid peroxidation ⁽²²⁾. The root extract of *Cassia auriculata* also reduces anti-TB drug induced liver toxicity by significantly lowering the levels of hepatic enzymes like **aspartate transaminase (AST)**, **alkaline phosphatase (ALP)**, **alanine transaminase (ALT)** and total bilirubin as well as cholesterol. Even the fruits of *Terminalia chebula* have similar functions ⁽²³⁾. Thus, some phytochemicals reverse the effects of synthetic drugs and reduce the toxic impact on liver (Figure 1).

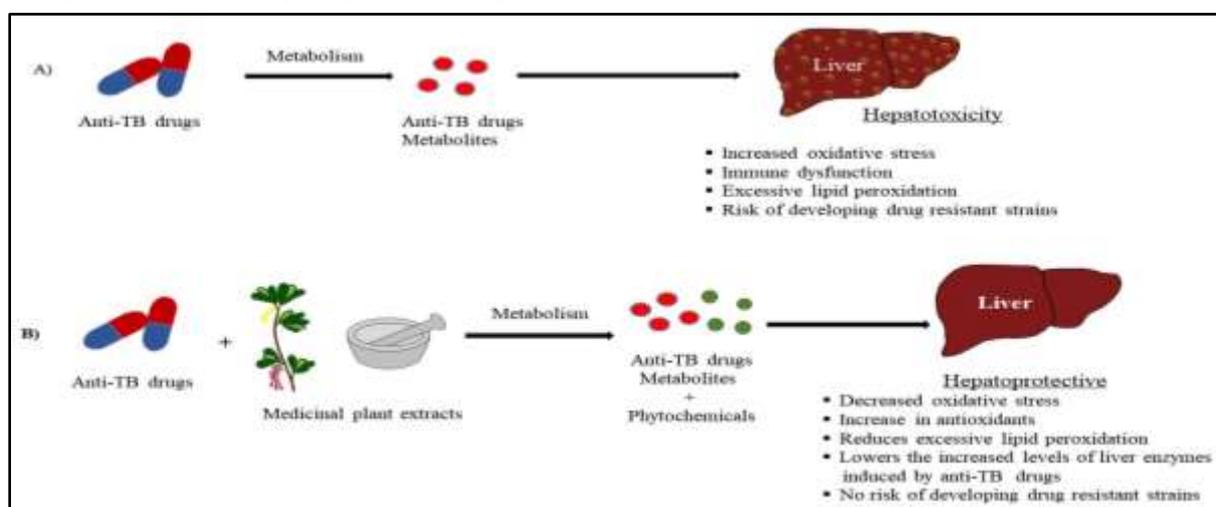


Figure 1. Hepatoprotective role of phytochemicals against synthetic anti-TB drugs (Adapted from Mangwani et al, 2020) ⁽²⁴⁾

Like synthetic anti-TB drugs, phytochemicals interfere with cellular mechanisms of mycobacteria and inhibit their growth. However, because exposure to phytochemicals does not lead to development of resistance in mycobacteria⁽²⁵⁾, there is a negligible risk of drug-resistant strains developing after or during TB therapy using plant

molecules. The recent research in this area has given us hope for improving the strategies to combat tuberculosis. Several such potential anti-TB phytochemicals have already been identified and their actions have been tested^(26,27,28). Some of the potential anti-mycobacterial phytochemicals have been listed in table 2.

Table 2. Phytochemicals having potent anti-TB activity

S. No.	Phytochemicals	Activity	Isolated from Plants	References
1	1 α -Acetoxy-6 β , 9 β -dibenzoyloxy-dihydro- β -agarofuran	Against MDR strain of <i>Mtb</i>	<i>Celastrus vulcanicola</i> Donn. Sm. (Celastraceae)	(29)
2	5-Hydroxy furanocoumarin	Against MDR strain of <i>Mtb</i>	<i>Foeniculum vulgare</i> Mill. (Apiaceae)	(30)
3	5-hydroxy-2-(4'-hydroxyphenyl)-7-methoxy-2,3-dihydro-4H-chromen-4-one	Against <i>Mtb</i> H37Rv	<i>Phoradendron robinsoni</i> Trel. (Santalaceae)	(31)
4	5,7-dihydroxy-3-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one; β,γ -dimethyl- α,δ -bis (3,4-dihydroxyphenyl) butane and 5,6,7-trihydroxy-3-methoxy-2-(4-methoxyphenyl)-4H-chromen-4-one	Against <i>Mtb</i>	<i>Larrea divaricata</i> Cav. (Zygophyllaceae)	(31)
5	(14b, 24E)-3-oxolanosta-7,24-dien-26-oic acid (MIC=64 μ g/ mL), and (14b, 24E)-3-hydroxylanosta-7,24-dien-26-oic acid	Against <i>Mtb</i> H37Rv	<i>Amphipterygium adstringens</i> (Schldt.) ex Standl. (Julianaceae).	(31)
6	25-Hydroperoxycycloart-23-en-3 β -ol	Against MDR strain of <i>Mtb</i>	<i>Blepharodon nitidum</i> (Vell.) J.F. Macbr. (Asclepiadaceae)	(32)
7	Abietane and its derivatives	Against MDR strain of <i>Mtb</i>	<i>Plectranthus grandidentatus</i> Gurke (Lamiaceae)	(33)
8	Aristolactam I, alkaloids, nitro compounds, and triterpenes	Against <i>Mtb</i> H37Rv	<i>Aristolochia brevipes</i> Benth. (Aristolochiaceae)	(34)
9	Azorellanes; azorellanol	Against MDR strain of <i>Mtb</i>	<i>Azorella compacta</i> Phil., <i>A. madreporica</i> Clos. (Apiaceae)	(35)
10	Beilschmin A	Against MDR strain of <i>Mtb</i>	<i>Beilschmiedia tsangii</i> Merr. (Lauraceae)	(36)
11	Calanolide A, B, and soulatrolide	Against <i>M. tuberculosis</i>	<i>Calophyllum brasiliense</i> Cambess. (Clusiaceae)	(37)
12	Coumarins, marmelosin, marmin, xanthotoxol, kaempferol 3 Orhamnoside and afzelin	Against <i>Mtb</i> H37Rv and <i>M. bovis</i>	<i>Aegle marmelos</i> L	(28)
13	Dibenzocyclooctadiene lignans Polysaccharides	Inhibit HIV replication; Inhibit <i>Mtb</i> H37Rv	<i>Schisandra chinensis</i>	(38, 39)

Counited table (2)

14	Dihydro- β -agarofuran sesquiterpenes (1 α -acetoxy-6 β ,9 β -dibenzoyloxy-dihydro- β -agarofuran)	Anti-TB activity against the MDR strain	Leaves of <i>Celastrus vulcanicola</i> Donn. Sm. (Celastraceae)	(29)
15	Diospyrin	Against MDR strain of <i>Mtb</i>	<i>Euclea natalensis</i> A.DC. (Ebenaceae)	(40)
16	Diterpene (<i>E</i>)-phytol; triterpenes: cycloartenol, sitosterol, stigmaterol, epidioxysterol; ketosteroids: stigmasta-4-en-3-one and stigmasta-4-22-dien-3-one	inhibit <i>Mtb</i> H37Rv strains	<i>Morina citrifolia</i> Linn.	(41)
17	Ethyl <i>p</i> - methoxycinnamate	Against MDR strain of <i>Mtb</i>	<i>Kaempferia galangal.</i> L. (Zingiberaceae)	(42)
18	Eupomatenoid-5, a neolignan	Inhibit <i>Mtb</i> H37Rv	<i>Piper regnellii</i>	(14)
19	Fargesin; (8R,8 R, 9R)-cubebin	Against MDR strain of <i>Mtb</i>	<i>Aristolochia elegans</i> Mast (Aristolochiaceae)	(43)
20	Glabridin, hispaglabridin B	Antitubercular activity against isoniazid resistant <i>Mtb</i> , avirulent H37Ra & H37Rv	<i>Glycyrrhiza glabra</i>	(44)
21	Glycyrrhizin	Antitubercular activity against isoniazid resistant <i>Mtb</i> , avirulent H37Ra, H37Rv; isoniazid monoresistant and isoniazid polyresistant strains of <i>Mtb</i>	<i>Glycyrrhiza glabra</i>	(45)
22	Hydroxychavicol acetate, 4-allylcatechol, <i>trans</i> -caffeicaldehyde	Inhibit <i>Mtb</i> H37Rv	<i>Piper taiwanense</i>	(14)
23	Isoxazole analogs of curcuminoids	Against MDR strain of <i>Mtb</i>	<i>Curcuma longa</i> L. (Zingiberaceae)	(46)
24	Licarin A, Licarin B and Eupomatenoid-7;	Against <i>Mtb</i> H37Rv and <i>M. avium</i> ;	<i>Aristolochia taliscana</i> Hook. & Arn. (Aristolochiaceae)	(34)
25	Oleanolic acid	Against MDR strain of <i>Mtb</i>	<i>Lantana hispida</i> Kunth (Verbaseae)	(47)
26	Oleanane triterpenoid aegicerin	Against MDR strain of <i>Mtb</i>	<i>Clavija procera</i> B. Stahl (Theophrastaceae)	(48)
27	Naphthoquinones, plumbagin and its dimers marinone and 3,3'-biplumbagin	Strongest activity against <i>Mtb</i> strains	<i>Diospyros anisandra</i> S.F.Blake (Ebenaceae)	(49)
28	Piperine (an alkaloid)	Inhibits multidrug efflux pump (Rv1258c) in <i>Mtb</i>	<i>Piper nigrum</i> L.	(50)
29	Plumericin	Against sensitive as well as four MDR strains of <i>Mtb</i>	<i>Plumeria bicolor</i> Ruiz & Pav. (Apocynaceae)	(51)
30	Silymarin consisting of flavonolignans, mainly silybinin, silydianin and silychristin	Administered in case of liver injuries	<i>Silybum marianum</i> (L.) Gaernt. (Sm)	(14)
31	Tiliacorinine, 2'-nortiliacorinine, tiliacorie	Against MDR strain of <i>Mtb</i>	<i>Tabernaemontana elegans</i> Stapf. (Apocynaceae)	(52)

Counited table (2)

32	Thymoquinone	Inhibits <i>Mtb</i> H37Rv and <i>Mtb</i> XDR-TB	<i>Nigella sativa</i> L. (Black cumin)	(14)
33	Ursolic acid, hydroquinone	Against MDR strain of <i>Mtb</i>	<i>Artemisia capillaris</i> Thunb. (Asteraceae)	(53)
34	Ursolic acid	Against MDR strain of <i>Mtb</i>	<i>Chamaedorea tepejilote</i> Liebm. (Palmae)	(54)
35	Ursolic acid, cucurbitacin E2-0-β-d-glucopyranoside	Against MDR strain of <i>Mtb</i>	<i>Citrullus colocynthis</i> (L.) Schrad. (Cucurbitaceae)	(55)
36	Vasicine acetate; 2-acetylbenzylamine	Against MDR strain of <i>Mtb</i>	<i>Justicia adhatoda</i> L. (Acanthaceae)	(56)
37	Compounds having lipophilic fatty acid groups	Against <i>Mtb</i> H37Rv	<i>Costus speciosus</i> , <i>Cymbopogon citratus</i> and <i>Tabernaemontana coronaria</i>	(57)

Lately, Sarangi et al. ⁽⁵⁸⁾ (2021) have listed Indian ethnomedicinal plants having potent antimycobacterial and immunomodulatory activity. Many of these plants have been mentioned in our ancient texts and among those, the plants having anti-TB activity are *Allium sativum* L, *Piper* Sp. L, *Cinnamomum verum*. J. Presl, *Tinospora cordifolia* (Thunb.) Miers and *Shorea robusta* Roth. Flowers of *Dodonaea viscosa* L. Jacq., a native plant to Asia, Africa and Australia, show anti-mycobacterial activity against three strains of M.tb i.e. bg1972, H37Rv and Bg206⁽⁵⁹⁾. Another plant that can provide molecules which may be used in managing TB is *Sansevieria liberica*. Its rhizomes show activity against M.tb at 1 mg/ml ⁽⁶⁰⁾. *Vitellaria paradoxa* has been traditionally used in Cameroon to treat TB. *In vitro* study has shown the antimycobacterial activity of bark extracts of *V. paradoxa* and *Alstonia boonei* against H37Rv ⁽⁶¹⁾.

Anti-TB phytochemicals and their mode of action

Much research has been done to identify phytochemicals which might prove useful in curing or improving the efficacy of TB treatment. Phytochemicals might work wonderfully when used with synthetic anti-TB drugs to ameliorate the side effects associated with these drugs. They might do so by disrupting intracellular cell signalling systems. Different phytochemicals use different modes of action to reduce the cell damage or abnormal cell response, however, primarily they do so by decreasing oxidative damage and modulating the inflammatory response. Phytochemicals are strong antioxidants. They capture free radicals, reduce excessive lipid peroxidation in liver and also lower the activity of enzymes such as alanine transaminase (ALT), alkaline phosphatase (ALP) and aspartate transaminase (AST), while the antioxidant enzymes activity as catalase, superoxide dismutase and glutathione is increased. All of these activities

contribute to the hepatoprotective role of phytochemicals ^(14,62). It is worth noting that hepatotoxicity caused by anti-TB drugs is one of the causes of TB morbidity and mortality ⁽⁶³⁾.

Some of the commonly used plants that reduce hepatotoxicity include Garlic (*Alium sativum*), onion (*Alium cepa*), *Terminalia chebula* fruit, sylimarin isolated from milk thistle (*Sylibum marianum*) and curcumin. Two constituents of garlic viz. diallyl disulfide and diallyl trisulfide upregulate the activity of glutathione-S-transferase, a potent antioxidant enzyme. Ginger, *Zingiber* (Zingiberaceae), has been used traditionally to cure the symptoms associated with TB in Uganda and Ghana ^(14,64). *Bacopa monnieri* (Brahmi) may be used as a supplement with INH and RIF, as anti-TB treatment regimen, as it reduces the oxidative stress caused by anti-TB drugs in the kidneys ⁽¹⁰⁾.

Curcumin is a phytochemical derived from *Curcuma longa* rhizomes. It protects the liver cells from oxidative damage by acting as an antioxidant. It accomplishes this by activating the Keap1/Nrf2 pathway, suppressing the expression of NADPH oxidase in the liver (a potent source of ROS), activating the enzymes heme oxygenase-1 and NAD(P)H quinone dehydrogenase-1, and lowering the expression of cytochrome P450 2E1 (CYP2E1) and peroxiredoxin 1 (Prx1) (increased expression of both is a potent source of ROS). Keap1/Nrf2 pathway is a major regulatory pathway that protects cells from oxidative stress induced by endogenous and external ROS, as well as electrophiles ⁽⁶⁵⁾. NAD(P)H quinone dehydrogenase-1 (NQO1) catalyses the conversion of quinones to hydroquinones, which is vital for detoxification ⁽⁶⁶⁾. Quinones are intermediates in the production of reactive oxygen species (ROS) ⁽⁶⁷⁾. The physiological stress, due to anti-TB drugs, triggers the activation of heme oxygenase-1 (HO-1) which

protects the cells from oxidative damage. Other than curcumin, several other plant molecules are potent inducers of HO-1 and consequently cytoprotective when administered with anti-TB drugs. These include quercetin (from fruits and vegetables), resveratrol (from fruits and vegetables), epigallocatechin gallate (EGCG) (green tea), garlic-derived organosulfur compounds: diallyl sulphide (DAS), diallyl disulphide (DADS), diallyl trisulphide (DATS), S-allyl-cysteine (SAC) (from *Allium sativum*, mustard and *Ferula asafoetida*) and isothiocyanates (sulforaphane, phenethyl isothiocyanate, allyl isothiocyanate) (from Cruciferous vegetables)⁽⁶⁸⁾.

Curcumin is also anti-inflammatory as it downregulates the expression of toll-like receptors (TLR2, TLR4) and nuclear factor kappa light chain enhancer of activated B cells (NF- κ B)^(69,70). TLR4 and TLR2 are pattern recognition receptors (PRRs) which recognize microbial molecules, on pathogen surfaces known as pathogen-associated molecular patterns (PAMPs). This interaction triggers production of ROS and an inflammatory response. During signaling, all the TLRs including TLR4 and TLR2 converge at NF- κ B, a pro-inflammatory molecule, and exert their effects^(71,72). PAMP-PRR interaction is a crucial event in innate immunity, and overstimulation caused by anti-TB drugs can result in severe inflammatory responses and its associated symptoms. *In vitro* studies have shown that demethoxycurcumin and bisdemethoxycurcumin, present in curcumin, also inhibit the growth of *M.tb*, *M. marinum* and rifampicin-resistant *M.tb* strains. The most powerful phytochemical among these is demethoxycurcumin⁽¹⁴⁾.

Silymarin, the seed extract of *Silybum marianum*, is also known to be hepatoprotective. Silymarin is a flavanoid complex which contains silybin, silydianin and silychristin. It protects the liver cell as it stabilizes the membrane potential and restores the functions of the liver enzymes by regulating the aberrant increase of the enzymes like AST and ALT. When used with other anti-TB drugs, silymarin significantly reduces liver damage. It acts as anti-inflammatory compound also as it inhibits the expression of inflammatory genes like NF- κ B, intercellular Adhesion Molecule 1 (ICAM-1) and interleukin-6 (IL-6). Similarly, bicyclol, a schisandrin C analogue, from *Schisandra chinensis* protects the liver against anti-TB drug-induced liver damage by lowering increased levels of liver enzymes such as AST, ALP, and ALT. Bicyclol is more powerful of the two⁽⁷³⁾.

Piperine is an alkaloid extracted from the plants of Piperaceae family. Piperine significantly reduces the *M.tb* bacilli load when co-administered with rifampicin as compared to when rifampicin is administered alone. Piperine stimulates killing of MDR-*M.tb* by inhibiting P-glycoprotein of pathogen. It is a suitable candidate to be considered

for developing bioactive drug molecules as it has no related toxicity⁽¹⁴⁾. Another phytochemical which may be considered for TB treatment is withanolide, extracted from the plant *Withania somnifera*. It has antioxidant properties and protects the liver cells by reducing hepatocyte necrosis, levels of serum ALT and intrahepatic haemorrhage as has been observed under *in vitro* conditions⁽²¹⁾.

Quercetin is a polyphenolic flavonol found in plants such as *Vitis vinefera*, *Allium cepa*, and *Camellia sinensis*. By altering intracellular signalling pathways such as the nuclear factor erythroid 2-related factor 2/HO-1 (Nrf2/HO-1) pathway, it protects hepatic cells from oxidative damage⁽⁷⁴⁾. *Ursolic acid* is a triterpenoid and is isolated from plants like *Mirabilis jalapa*, *Hedyotis corymbosa*, *Calendula officinalis*, *Bouvardia ternifolia* and *Byrsonima crassa*. It inhibits the formation of ROS by suppressing activation of mitogen-activated protein kinases (MAPKs), CYP2E1 and NF- κ B⁽²¹⁾. Berberine is another phytochemical isolated from plants such as *Berberis aristata*, *Coptis chinensis*, *Berberis aquifolium*, *Hydrastis Canadensis*, *Berberis vulgaris* and *Hydrastis canadensis*. It is an alkaloid which is an antioxidant and also has ameliorative effect on liver. It performs its functions by inhibiting microsomal drug-metabolizing enzymes. It also reduces oxidative stress by suppressing the expression of tumor necrosis factor- α (TNF- α), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) which results in decreased oxidative stress^(21,75).

Another potential effective anti-TB phytochemical is thymoquinone (TQ) which is isolated from seeds of *Nigella sativa*. It is a monoterpenoid and a good antioxidant. It increases the activity of enzymes including glutathione peroxidase (GPx) and superoxide dismutase (SOD), which protect liver cells from oxidative damage. It also serves as an anti-inflammatory agent as it inactivates expression of TNF- α , COX-2, iNOS and IL-1 β ^(76,77).

Stilbenes are extracted from plants like *Paeonia lactiflora*, *Vitis vinifera* and *Arachis hypogaea* and *in vitro* studies have shown that they possess hepatoprotective properties. Resveratrol (trans-3,5,4'-trihydroxystilbene,1), a type of stilbene, repairs the hepatic damage induced by RIF and INH. It does so by controlling the expression of Sirtuin1 (SIRT1), peroxisome proliferator-activated receptors (PPAR- γ) and peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α) mRNAs⁽⁷⁸⁾. High levels of SIRT1 increase oxidative stress but a moderate level is protective. SIRT1 regulates the acetylation of PGC-1 α . PGC-1 α is a transcriptional coactivator which binds to PPAR- γ , a nuclear receptor, to exert its effects. PGC-1 α then activates superoxide dismutase 2 (SOD2) and

glutathione peroxidase, both of which protect the cells from oxidative stress^(79, 80).

Andrographolide, isolated from *A. paniculata*, is another antioxidant and hepatoprotective phytochemical. It is a diterpenoid which reduces oxidative stress by upregulating the expression of hypoxia-inducible factor-1 alpha (HIF-1 α), SOD-1, HO-1 and glutathione S-transferase (GST). It inhibits the Notch-1/Akt/NF- κ B signaling pathway and thus acts as anti-inflammatory molecule^(81,82,83). When it interacts with glutathione (GSH), it induces expression of

CYP1A1^(81,82). CYP1A1 is a potent enzyme performing xenobiotic metabolism and thus, is involved in detoxification⁽⁸⁴⁾. Plumbagin is one of the most recent phytochemicals to be discovered. It shows anti-mycobacterial action and was isolated from *Plumbago indica* (also known as Chitrak in India). It works by blocking M.tb thymidylate synthase, an essential enzyme for the mycobacterium's survival⁽⁸⁵⁾. The chemical structures for selected phytochemicals are demonstrated in Figure 2.

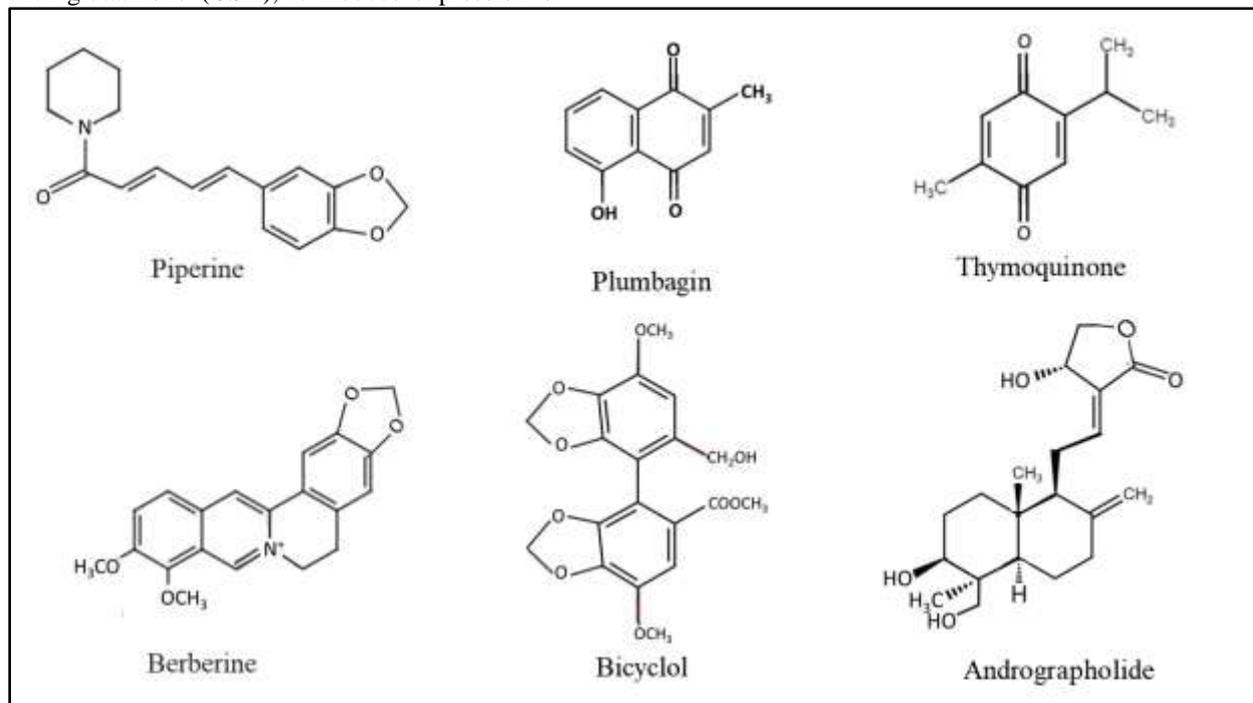


Figure 2. Chemical structures of some common phytochemicals

Phytochemicals and immune system

Phytochemicals not only act as antimycobacterial agents but also as agents that can boost immunity. Most of the studies that confirm the antimycobacterial activities of the phytochemicals have been performed *in vitro*. The effects of phytochemicals might vary if they are administered *in vivo*. This is because many factors including the immune system, influence the activity of phytochemicals *in vivo*. When combined with anti-TB drugs, phytochemicals or plant extracts work as adjuvants, and the treatment is more effective as they not only reduce anti-TB drugs adverse effects, but also alleviate synthetic drug functions and boost the immune system's ability to fight M.tb^(14,86). Like other microbial infections, the mycobacterial infection too is accompanied by inflammation in the early stages and later it activates an adaptive immune response. Innate immune cells primarily macrophages, monocytes, dendritic cells and neutrophils, play a critical role in the early progression of TB infection. M.tb suppresses immune response against itself. The interaction of

M.tb with the body's immune system is complicated by the anti-TB drugs, which increase the host's susceptibility to reinfection. Thus, if anti-inflammatory drugs are administered along with the designated treatment regimen for TB it will improve treatment efficacy⁽¹⁴⁾.

Since there is only one vaccine available for TB, plant products, can be used as immunomodulators to increase immunity, which could help to improve therapeutic efficacy of anti-TB drugs without too many adverse effects. Piperine, quercetin, genistein, plumbagin, caffeic acid, lupeol, ursolic acid, oleanolic acid, stigmasterol, β -sitosterol, and betulinic acid are some of the important phytochemicals with immunomodulatory activity. Extracts from plants like *Aegle marmelos*, *A. sativum*, *Andrographis paniculata*, *Calophyllum brasiliense*, *Centella asiatica*, *Glycyrrhiza glabra*, *Adhatoda vasica*, *Ocimum basilicum*, *Stachytarpheta cayennensis*, *Withania somnifera* and *Urtica dioica* L. show immunomodulatory activity⁽⁸⁶⁾.

Alcoholic extract of Miana (*Coleus scutellarioides*) leaves has anti-M.tb activity, which is attributed to increased host immunity rather than direct suppression of the mycobacteria. Garlic extract has a similar mode of action. Allicin present in garlic activates SAPK/JNK pathways, causing macrophages to produce less TNF- α (a key mediator of the inflammatory response). Sylimarin keeps M.tb infection in check indirectly through activating expression of IFN- γ , IL-12 and TNF- α , when administered alone or in combination with synthetic drugs. Piperine enhances splenocytes as well as humoral and cell-mediated immune responses, when given in combination with rifampicin, by activating Th-1, IFN- γ and IL-12. The aqueous extract of *Phyllanthus niruri* activates cells and molecules involved in inflammatory response, killing microbes and lowering mycobacterial load in tuberculosis patients. It does so by activating phagocytic cells like macrophages and mononuclear cells and increasing the levels of IFN- γ and TNF- α ⁽¹⁴⁾.

The plant extracts also induce expression of surface molecules on macrophages which stimulate immune response. The macrophages release pro-inflammatory cytokines and also forage free radicals. M.tb's intracellular survival is reduced by these actions. Curcumin also influences the immune system's ability to fight M.tb. It restores memory immune response and prevents reinfection of M.tb by controlling inflammation and immune response ⁽¹⁴⁾. D-Pinitol, also known as 3-O-methyl D-Chiro inositol, is an antioxidant, anti-inflammatory, antimycobacterial, and immunosuppressant derived from *Acacia nilotica*, *Aegle marmelos*, and *Glycyrrhiza glabra*. It acts synergistically with INH and RIF ⁽²⁸⁾. Thus, using plant-based products in combination with synthetic drugs for the treatment schedule of TB is a better treatment strategy as it increases the efficacy of treatment and also reduces its duration ⁽¹⁴⁾.

Conclusion

Plants have great potential to be used in the treatment strategies of many diseases including tuberculosis. There have been many studies on plant-derived biomolecules to be used for treating TB. The properties of phytochemicals that make them attractive for TB treatment include their antioxidant activity, anti-inflammatory activity, anti-mycobacterial activity, their ability to boost the immune system, no side-effects, etc. Innumerable phytochemicals have been isolated and tested for different properties, nonetheless, still a lot needs to be explored. However, the major concern is that most of these properties have been observed in *in vitro* studies. The *in vivo* action of these biomolecules still needs to be explored extensively before some of these biomolecules can be made part

of alternative medicine and made available for TB treatment.

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