http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v13i03.03

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Deep Insight to Mycobacterium Tuberculosis (Mtb): Causes, Symptoms, Diagnostics, Treatment, Risk Assessment, Recent Advances & Role of Natural Products

Author
Sripathi Chandragupthan*

Abstract
Nearly ¼ TH of world's population is affected by the bacteria that is causing TB, but only 1/10 TH of them affecting TB disease called "Mycobacterium Tuberculosis" (Mtb). It can be two forms namely active and latent. Tuberculosis is ranked by WHO as "One of the top 10 leading causes of death". This is true both before and after COVID-19 pandemic[3]. This paper discusses about TB causes, microscopic analysis, Infection, symptoms, diagnosis, treatment, complexities and role of natural product.
Key Words: *TB, M Tuberculosis, Drug Resistance TB, TB infection with co-infection, Natural products.*

Introduction

Johann Schonlein coined the term "tuberculosis" in the 1834, though Archaeologist have found TB in the bones of ancient bison in Wyoming. These bison lived over 17,000 years ago. Tuberculosis (TB) was named "phthisis" in ancient Greece, "tabes" in ancient Rome, and "schachepheth" in ancient Hebrew. *Mycobacterium tuberculosis (Mtb)* was discovered by Dr. Robert Koch on 24TH March 1882[1,2].

Background & Microscopic Review

Mycobacterium tuberculosis is the etiologic agent of tuberculosis (TB) in humans. Humans are the only reservoir for the bacterium. Mycobacterium bovis is the etiologic agent of TB in cows and rarely in humans. Both cows and humans can serve as reservoirs for Mycobacterium bovis. Humans can also be infected by the consumption of unpasteurized milk. Mycobacterium Tuberculosis is aerobic, non-sporing, non-motile and non-Capsulated bacteria. They measure 0.5um X 3um in size. It can appear straight or slightly curved thin rod-shaped bacilli and live in single, pairs or small chumps. Since it is aerobic, prefers to go to lungs. It can divide in 18 – 24 hours. It falls under the category of mycobacterium because it had mycolic acid in its cell wall. Mycolic acid is rich in lipid. This makes it resistant to gram stain. That why it is also called acid fast bacilli. It can survive against week disinfectants[4]. It needs oxygen to grow, and it falls into category of "Aerobic Bacterium" that's why it prefers to go to lungs and it only travels through air by cough.

The cell wall envelope of mycobacteria is structurally distinct from that of both Gram-positive and Gram-negative bacteria. In Mycobacterium tuberculosis, this cell wall has unique structural features and plays a crucial role in drug resistance and macrophage survival under stress conditions. Peptidoglycan is the major constituent of this cell wall, with an important structural role, giving structural strength, and counteracting the osmotic pressure of the cytoplasm. Synthesis of this complex polymer takes place in three stages that occur at three different locations in the cell, from the cytoplasm to the external side of the cell membrane, where polymerization occurs. A fine balance of peptidoglycan synthesis and degradation is responsible for a plethora of molecular mechanisms which are key to the pathogenicity of Mycobacterium tuberculosis (Mtb). Enlargement of mycobacterial cells can occur through the synthesis of new peptidoglycan, autolysis of old peptidoglycan, or a combination of both processes[4].

Transmission

Mycobacterium tuberculosis is transmitted normally by air-borne route. When infected person with active TB disease talks, sings, coughs, sneezes, etc droplets containing the Mtb is expelled into the environment and the person who inhales it gets infected. However, concentration of mycobacterium in the droplets, frequency and strength of cough, dilution of the droplets in the atmosphere, exposure in the sun light, frequency and strength of the exposure, ventilation, virulence of the strain of mycobacterium tuberculosis exposed in atmosphere, duration of the exposure, are some of the important factors determining the transmission. Usually after transmission, it does not become active and will be latent inside the lungs. When it gets opportunity such as immunosuppression in become active. It rarely become active after transmission. Therefore, a person with latent TB cannot spread the mycobacterium whereas the person with active TB can spread the mycobacterium[5].

Pathophysiology

Primary infection prefers to go lower lobe of lung but latent infection prefers upper lobe since upper lobe has high V / O ratio (ratio between ventilation and absorption of oxygen in blood). As soon as the mycobacterium enters the lung alveolar macrophage phagocytose it. Due to its various virulence factor, the macrophage is unable to digest the mycobacteria. Mycobacterium tuberculosis has three major virulence factors namely, catalase peroxidase, sulfides and trehalose dimycolate. Catalase peroxidase prevents oxidation of cells. So the mycobacterium grows inside the macrophage and then kills the macrophage. After some time the macrophage blasts and the mycobacterium get spread to the whole lung which results granuloma formation. Granuloma is bacteria surrounded by all immune cells. It is a step-in order to prevent spreading of the infection. After this the lung tissue inside the granuloma dies which is called ghon focus caseating necrosis, the mycobacterium may travel to near lymph node and caseating necrosis may occur there. Lymph necrosis in addition to Ghon Focus is known as Ghon complex. Ghon complex may undergo fibrosis and calcification to form scar tissues. This stage is called Ranke complex. From there are two ways to proceed further. One way is immune system clears the infection successfully. The other is it may become latent and after getting immunosuppression becomes reactivated. Memory T cells release cytokines as an attempt to contain the mycobacteria. But this result to mere caseating necrosis in the lung. Now the infection gets dispersed throughout the lung. It may go to lymphatics and spread cell over the lungs. This may cause bronchopneumonia. These mycobacteria may also spread through lymphatic system and vascular system to all parts of our body. This is called miliary TB. It affects macrophages and can go into other cells when

required. It produces catalase peroxidase which prevents oxidation of cells. It produces sulfide that affects macrophages and prevents phagosome activation and phagosome lysosome fusion. It also produces trehalose dimycolate which evades immune response, cytokine release and granuloma formation. It has long pathogenetic chain. It may also spread to other parts which is called Miliary TB. Patients should be tested for TB before giving immunosuppressant drugs. The central necrosis in granulopoiesis promotes mycobacterium transmission is hallmark characteristics of sever TB cases. One of the recent studies reveals that mycobacterium tuberculosis induced necrosis accelerates the growth of the bacteria within dead cell. Hence, Mycobacterium tuberculosis (Mtb) induced cell death plays an important role in the pathogenesis. Mycobacterium tuberculosis (Mtb) Caused granulomatous inflammation's patterns are Necrotizing and Non-Necrotizing granulomas[1,6,7].

TB Prevention

TPT is a drug or a set of drugs which is used to protect someone from TB infection. It does not work during TB disease. This is being given first to the risky population who have higher risk of getting infected with TB infection and easily progress from infection to disease.

BCG (bacillus Calmette-Guerin) vaccination plays a critical role in the preventive management, however difference in opinion is raised by experts on the efficacy of the BCG. WHO recognises the efficacy of the BCG. It is widely accepted that it reduces the risk of childhood TB with an 85% reduction in TB meningitis and miliary TB[8]. Vaccination can be classified into preventive Pre-exposure, Post exposure and therapeutic. Vaccines can also be classified based on their biochemical forms namely live attenuated, inactivated, protein subunit or recombinant which targets various cells or subcellular components of TB pathogenesis[9]. About two dozen of tuberculosis vaccines are under various stages of trail which gives hope for the possible future vaccine with improvised protection. Some of the promising candidates are MIP, RhMCV,ChadOx1 / PPE15, AEC/BC02, H1:IC31, M72/AS01E, RUTI, BCG – Zmp 1, SapM, CysVac2, VMP1002, Ad5-CEAB, Ad35, GaM.tb, H4:IC31, H56:IC31, ID93/GLA-SE, DAR, MTBvac, V7, Vaccae, DAR-901, Immuvac, MVA84A,AD5Ag85A, etc[10].

Screening & Diagnosis Methods

Screening

There are more than 40 tools for screening namely symptoms screening and chest radiography, c-reactive protein, and rapid molecular test available. Symptom screening involves checking a person for TB symptoms and TB symptom include weight loss, hemoptysis, fever, high heart rate and respiratory rate [1,11-16]. The symptoms screen is summarised in the table-I below. Clinician shall exercise caution on symptoms which can mimic age related illness, or some patients may not exhibit critical symptoms.

Table I: Symptom Screening Summary Table

TB Type	Symptoms
Latent	
Latent	No symptom
Active TB Based on Body Part Affected	
Pulmonary TB	Cough with or without blood / phlegm, chest pain, shortness of breath.
TB Lymphadenitis	Fever, Fatigue, Unexplained weight loss, Night sweats, Swollen Lymph nodes.
Skeletal TB	Active TB symptoms, Severe back pain, Stiffness, swelling, abscesses, bone deformities
TB Pericarditis	Chest pain. Fever, Palpitation, Shortness of breath, cough
Cutaneous TB	Lesions (flat, painless, purplish or brownish red, wart like appearance & small bumps and sores.
TB Meningitis	aches, Pains, loss of appetite, Persistent headache, low grade fever, nausea, vomiting, severe headaches, sensitivity to light, neck stiffness
Gastrointestinal Tract TB	Nausea, Vomiting, Loss of appetite, fever, ascites buildup of fluids in the abdomen (abdominal swelling, bolting & tenderness), abdominal pain, changes in bowel habits, abdominal mass which can be felt.
Liver TB	Liver enlargement, Jaundice, High grade fever, upper abdominal pain,
Genito urinary TB	Testicular swelling, Painful urination, decreased or interrupted flow of urine, pelvic pain, back pain, decreased semen volume, infertility.
TB Lymphadenitis	Fever, Fatigue, Unexplained weight loss, Night sweats, Swollen Lymph nodes.
Transverse Myelitis	Weight loss, asthenia, intermittent fever, night sweat, lower limb weakness, neck stiffness, positive Brudzinski and Kernig's sign, areflexia lower limbs, paraparesis, severe headache, inability to walk, urinary incontinence.
TB-IRIS	Shortness of breath, cough, fever, weight loss, night sweat.
Miliary TB	Fever of several weeks duration with morning temperature spikes, anorexia, weight loss, lassitude, dry cough with phlegm, coughing up blood in phlegm, night sweat, skin reactions, abdominal pain, symptoms of hepatosplenomegaly

Diagnosis

Radiographical tools and laboratory test tools can be effectively used along with clinical trial, pros, and cons of various radiographical, and laboratory test tools are presented in the table-II. Chest X-ray is highly sensitive tool. Artificial Intelligent (AI) backed advanced radiography machines can identifies abnormalities. C-Reactive Protein is a general marker of inflammation in the body. Rapid Molecular Test is less sensitive tool and requires follow up test. Access for the diagnostic test to be ensured.

Table II: Pros & Cons of Analytical tools

Test	Pros	Cons
Tuberculin skin test	High specificity in non-BCG-vaccinated populations	Training required for administration and interpretation
	Cost-effectiveness	Return visit required in 48–72 hours for test result
		Possible false-positive and false-negative results
Interferon-γ release assay	High specificity	Blood withdrawal required
	Only one patient visit required	Indeterminate results in those who are immunosuppressed
	Results available in 16–24 hours	No capacity to differentiate between latent and active TB
	No confounding by BCG vaccination	High cost
Chest radiography	Ready availability	Low sensitivity and specificity
	Capacity to differentiate latent infection from active TB	Not confirmatory
Smear microscopy	Ease, speed, and cost-effectiveness of the technique	Low sensitivity
	Quantitative estimate of the number of bacilli	No capacity to differentiate from nontuberculous mycobacteria
	Usefulness in determining infectiousness and in monitoring treatment progress	
Conventional culture using solid media	Examination of colony morphology possible	Wait of 3–8 weeks for result
	Quantitative results	
Automated liquid-culture systems	Sensitivity greater than culture in solid media	Contamination-prone
	Faster results (1–3 weeks)	Stringent quality-assurance systems required
		Expensive equipment required
Nucleic acid amplification test (NAATs)	High specificity	Low sensitivity with smear-negative TB
	Higher sensitivity than smear microscopy	Contamination-prone
	Rapid (1–2 days) diagnosis	Technical skill and expertise required
	Capacity to differentiate TB from other mycobacteria	High cost

TB Classification and Treatment:

TB can be classified into three, namely Drug susceptible, drug resistance and miliary. Drug resistance can be further classified into five, namely mono drug Resistant, Poly Drug Resistant, Multi Drug Resistant (MDR-TB), Pre-Extensively Drug Resistant (Pre-XDR TB) and Extensively Drug Resistant (XDR-TB). Miliary TB occurs when bacilli enter the bloodstream and dispersed throughout the body. It is rare and risk to life. Treatment shall be in accordance with WHO guidelines or local health authority guidelines. Effectiveness of the TB treatment is depending on prompt diagnosis of TB, recognition of drug resistance, patient's adherence on drug regimens, contact tracing and prophylactic treatment of contacts, screening of TB infection in high-risk group. Patients with co-infection and co-morbid disease often call for multidisciplinary comprehensive support and treatment [10,12,14,17-20].

Role of Nutrition:

Lack of nutrition in the body leads to blunt immune response on pathogens. This is a very dangerous to them because nothing will be there to destroy the pathogen. A study showed that vitamin A deficiency in household contacts increased 10 times progression from infection to

disease. It also showed that vitamin E and D deficiency increased 2 times and 5 times chances of progression from infection to disease respectively[21,22]. Body Mass Index (BMI) plays an important role in this. Multiple studies shows that undernutrition likely increases severity and worsens treatment outcome. Zinc protects our body from free radicals and prevents lung damage by hypoxia[23,24]. Table-III represent the simplified clinical interpretation of BMI index; caution should be exercised by the clinician based on clinical trial and other analytical results.

Table-III: Clinical Interpretation

BMI, Kg/m^2	Interpretation
<16	Undernutrition
16 – 15.9	Moderate undernutrition
17 – 18.5	Mild undernutrition
25 - 30	Over-weight
>30	Obese

Discussion & Results Analysis

Lab analysis along with clinical trial can be corelated with epidemiological data to get an insight on adverse side effects, drug interaction, concurrent diseases, etc should be considered for the development of the treatment plan. The following factors plays a critical role in the risk assessment of MDRTB[19].

- Exposure to known MDR – TB patients
- HIV co-infection / patient with immune suppression treatment, diabetes, malnutrition.
- Healthcare providers with high prevalence of MDR-TB
- Discontinued treatment with first line regimen
- Failure to respond to first line regimen.
- Relapse after a full course of treatment with first line regimen.
- Living in aerosol countries with high prevalence of MDRTB

Management of side effects due to anti-TB drugs plays a vital role in the success of treatment. Second line anti-TB drugs have many side effects than first line anti-TB drugs. Manging the side effects is normal part of the treatment and it responsibility of clinician to diagnose and treat it. Suspending any drug due to side effects should be based on the weighting the risk of continued side effect against chances of curing a deadly disease. Nephrotoxicity, Hypothyroidism, neurotoxicity, electrolyte wasting (similar to Fanconi's syndrome) & ototoxicity due to injectables shall be monitored as part of the treatment. Second line drugs are known to cause birth defects, for this reason all women of childbearing age should use reliable method of contraception during multi drug resistant TB treatment. Capreomycin may increase risk of ototoxicity, may be used when necessary. Ethionamide generally avoided because of increased risk of nausea and vomiting associated with pregnancy. The risk of birth defects in MDR-TB treatment is highest in the first trimester of pregnancy, so the gestational age of the fetus shall be confirmed before taking these drugs. In some cases, mother does not accept the risk of the treatment and clinically stable, treatment can be delayed until the second trimester after comprehensive multidiscipline specialist opinion [4,17,19,20,25,26].

Pulmonary TB can be associated with various long-term complications such as scarring (fibrosis), bronchiectasis, chronic pulmonary aspergillosis (CPA), air way stenosis and chronic obstructive pulmonary disease (COPD). In one of the studies on 51 numbers of patient successfully treated with multi drug resistance TB, reveals 78% of them had persistent respiratory symptoms, 98% had residual radiological sequelae, 96% had ventilatory defects with 66% with ventilatory defects exhibiting a mixed type of ventilatory abnormality while 19% had pure restriction and 11% had pure obstruction after completion of treatment. Aspergillus lung disease may exhibit in three ways: Invasive Aspergillosis, a serious life-

threatening lung disease that present pneumonia; Allergic bronchopulmonary aspergillosis (ABPA) presenting as syndrome of severe asthma with fungal sensitization aften with central bronchiectasis and CPA which in post TB patients commonly present as an Aspergilloma / mycetoma. In post TB CPA, the fungus, most commonly Aspergillus fumigatus, colonizes cavities in the lung left behind by the TB[25,26].

Older TB patients may not exhibit classical clinical symptoms such as cough, hemoptysis, fever, night sweats or weight loss. Dyspnoea is more common, and haemoptysis is less common. The symptoms can mimic age related illness such as reduced functional capacity, chronic fatigue, cognitive impairment, anorexia, or pyrexia of unknown origin. It often difficult to obtain the basic data from elder patients due to poor memory, hearing, sight and speech difficulties [27,28,29].

Some studies report abnormal liver enzymes, hypoalbuminemia, hyponatraemia, hypokalaemia, and normocytic normochromic anaemia. One of the recent studies reveals increased mortality in older patients (28% in those ≥84 years) was observed within 60 days of treatment initiation and increased number of adverse events occurred in older patients despite the common practice of excluding the pyrazinamide (PZA) from initial regimen for many patients aged 80 years or above. It should be noted that immune system undergoes remodelling and decline as age advances. Special care to provide for elderly patients [19,28,29,35,36].

Central nervous system (CNS) TB is associated with high mortality and morbidity. Tuberculous myelopathy is rare form of neurological TB. Spinal cord involvement manifests like intramedullary tuberculoma, leptomeningitis, extradural TB and rarely transverse myelitis (TM). Direct bacillary invasion, vascular thrombosis, immunological mechanism, or mechanism related to treatment may cause TM. Transverse myelitis is a focal inflammatory disorder of spinal cord, often associated with infectious disease and can lead to permanent paraplegia or quadriplegia [17,32-34].

In Tuberculosis meningitis paradoxical inflammatory reaction are very difficult to predict and may result in morbidity and death. It is believed that the cause is excessive host immune response to dead or dying mycobacteria. Host directed therapies such as corticosteroids can reduce the cause of permanent neurological damages. However, detailed investigation shall be carried out before starting the treatment[33].

Peripheral neuropathy (PN) is a serious condition affecting the nerves are common for TB patients. In this condition nerves are affected, compromising the replay of information from different parts of body. It can affect sensory nerves, motor nerves or autonomic nerves. Causes of PN in patients with TB are TB itself, co-morbid conditions, malnutrition, diabetes mellitus, anti-TB medications, etc. Suspected patients need to be monitored carefully[31].

Another adverse effect of anti-TB drug is Tuberculosis -immune reconstitution inflammatory syndrome (TB-IRIS)[30]. It may occur during or even after completion of anti-TB therapy. It is an abnormal, excessive immune response against alive or dead mycobacteria tuberculosis that may occur in either HIV infected or more rarely uninfected patients. Paradoxical and unmasking forms are the most common forms of IRIS. Paradoxical IRIS is defined as recurrent, new, or worsening symptoms of treated case. Unmasking IRIS is an antiretroviral (ART) associated inflammatory manifestation of a subclinical infection with a hastened presentation. Pulmonary TB patients may exhibit paradoxical TB-IRIS as a worsening or recurrence of respiratory and constitutional symptoms and often new or expanding infiltrates on chest x-ray images. Lymph node paradoxical IRIS generally represent with rapid enlargement followed by suppuration. Neurological TB-IRIS generally presents with new or worsening meningitis and or features of raised intracranial pressure due to

enlarge cerebral tuberculomas or intracranial abscesses; mortality rate is high and can go up to 25%. It may also present with spondylitis, epidural abscesses and radiculomyelopathy. Abdominal TB-IRIS present as granulomatous hepatitis, retroperitoneal lymphadenopathy, and peritonitis whereas musculoskeletal form manifests as mano or poly polyarthritis. Unmasking TB-IRIS is not well defined, can vary in the degree of clinical presentation, two-third of unmasking form present with lung involvement, often severe pulmonary tuberculosis leading to acute respiratory distress syndrome or bronchiolitis obliterans organising pneumonia [37].

Miliary TB is common in infants and children younger than 5 years of age and immunocompromised persons which can be detected in the radiograph appearance of millet seeds scattered throughout the lung. Miliary TB may be found in individual organs including brain, several organs or throughout the whole body. Up to 25% of patients with miliary TB may have meningeal involvement[35].

Transplantation is available globally. Due to immunosuppression, transplant recipients are at high risk of re-activating latent TB from within themselves or from the transplanted donors. Several guidelines are available however precaution of TB infection of both donor and recipient to be checked[38,39].

Co-infection of parasitic diseases will normally increase the complication of TB treatment. Co-infections such as HIV, helminth increases the risk of active TB and aids progression of TB [40].

TB infection will be potential etiology for those have pulmonary diseases such as pneumonia, COPD and lung cancer. Auto-immune disease such SLE (systemic lupus erythematosus) and sarcoidosis will activate the TB because of immune suppressive therapy. The metabolic diseases such as diabetes mellitus, atherosclerosis and hypovitaminosis D will promote / increase the risk of TB progression [41].

A negative culture status six months after treatment initiation, no positive culture thereafter and no relapses within 1 year after treatment completion need to be confirmed for the cured cases of TB. Terminating the treatment in the mid will have adverse impact of health and will be the cause for MDR-TB [11].

Recent Advances

The use of host-directed therapeutics (HDTs) is intended to increase the success of TB treatment by immunomodulation and / or immune augmentation. Here, immunomodulation alludes to down-regulating non-productive inflammation and modifying immune response [42]. In contrast, immune augmentation is considered in the framework of synergizing with anti-TB treatment regimens of drug susceptible (DS) and drug resistant (DR) tuberculosis to improve long term outcome and promote cure. It should be noted that these approaches are at conceptual or laboratory level.

There are many drugs such as OTB-658, FNDR 20364, TB47, GSK839, MBX-4888A, TB-09, GSK-286, TBAJ-587, TBI-223, BVK-GSK098, GSK-286, Macozinone, TBAJ-587/ 876, / 976, TBI-166 / 223, BTZ-043, Delpazolid, GSK-656, OPC-167832, SPR720, SQ-109, Sutezolid, TBA-7371, Telacebec, delamanid, pretomanid, Sanfetrinem, Sudapyridine, clofazimine, Nix-TB, ZeNix, Simplici TB, TB-Practecal, etc. under various stages of trail promising the possible shorter treatment regime, reduced adverse side effects, decreased risk of relapse and evolution of drug resistance, etc [11,43- 47].

Role of Natural Products

Natural Products are gaining popularity as treatment to Tuberculosis. It has been used since ancient times by many. It can be used alongside anti-TB drugs to increase efficacy and patient survival. They help combat Tuberculosis as well as reduce side effects of drugs. They not only fight against Mycobacterium Tuberculosis but also

protects the body from damage caused by both immune responses and bacterial action. They contain many biologically active compounds, but the most researched compounds are flavonoids, terpenoids, alkaloids, Saponins, Glycosides, Tannins, and Phenolic compounds. They characteristically have multiple components, multiple targets and multiple interactions. They work in different ways but most of the pathways remain undiscovered[59]. Hepatotoxicity, the major off-target effect of anti-TB drugs, are treated with plants that are rich in Glycosides, flavonoids, triterpenes and phenolic compounds such as Moringa Oleifera[50]. Phytochemicals are listed in the table IV below along with its type, source and properties.

Table-IV: Phytochemical List

Phytochemical	Type	Source	Properties	Reference
Andrographolide	Diterpenoid	Andrographis Paniculata	Antioxidant, Hepatoprotective, Choleretic, Anti-Bacterial, Anti-Inflammatory, Antiviral, Antitumor, Antiasthma, Insecticidal Effects, Immunomodulatory, Inhibitory Effect On Mycobacterium Tuberculosis	50, 60
Berberine	Alkaloid	Berberis Aristate, etc	Antioxidant, Ameliorative Effects, Anti-Inflammatory, Immunomodulatory	50,60
Curcumine	Polyphenol	Curcuma Longa	Hepatoprotective Effects, Cellular Protection Against Oxidative Stress, Anti-Tumour, Anti-Inflammatory, Antioxidant, Antiviral, Anti-Liver, Fibrosis, Antiatherosclerosis, Anti-Alzheimer's Disease, Immunomodulatory Effects	50,59
Piperine	Alkaloid	Piper Longum, Piper Nigrum, etc	Anti-Inflammatory, Anti-Hepatotoxic, Anti-Tumour, Anti-Asthmatic, Anti-Analgesic, Anti-Depressant, Anti-Bacterial, Anti-Ulcer, Immunomodulatory Effects	50,60
Quercetin	Flavonoid	Vitis Vinifera, etc	Antimycobacterial Activity, Antibacterial Properties, Antitubercular Effects, Hepatoprotective Effects	50,59
Resveratrol	Polyphenol	Paeonia Lactiflora, etc	Antimycobacterial Effect	50,59
Silymarin	Flavonoid	Silybum Marianum	Hepatoprotective Properties, Antioxidant Effects, Increased Cell Membrane Stability, Anti-Inflammatory Properties	50
Thymoquinone	Monoterpenoid	Nidorella Anomala, Nigella Sativa, etc	Antioxidant Properties	50
Ursolic Acid	Triterpenoid	Bouvardia Ternifolia, Chamaedora Tepejilote, etc	Antitumor, Antidiabetic, Antiviral, Antibacterial, Anti-Inflammatory, Antioxidant, Anti-Inflammatory, Hepatotoxicity, Immunomodulatory Effects	50,60
Tanshinone	Diterpenoid	Salvia Miltiorrhiza	Anti-Inflammatory, Antioxidant, Anticancer, Antibacterial, Antitumor, Immunomodulatory Effects, Inhibitory Effects On Tuberculosis	60
Phloretin	Flavonoid		Anti-Inflammatory, Inhibitory Effect On Growth Of Mycobacterium Tuberculosis	59
Oxysophocarpine	Quinolizidine Alkaloid	Leguminosae Sophora	Analgesic, Anti-Inflammatory, Anti-Tumour	60
Bergenin	Polyphenol Compound	Bergenia Crassifolia, Etc	Immunomodulatory	60
Luteolin	Flavonoid	Reseda Odorata, etc	Immunomodulatory, Anti-Inflammatory, Anti-Allergic, Anti-Bacterial, Antioxidant, Anti-Tumour	60
Baicalein	Flavonoid	Scutellariae Radix	Anti-Bacterial, Anti-Inflammatory, Anti-Allergy, Anti-Tussive And Anti-Cancer	60
Isoliquiritigenin	Phenol	Glycyrrhiza Uralensis	Anti-Tumour, Anti-Inflammatory, Antioxidant	60
Tea Polyphenol	Flavonoids	Tea	Damages Cell Wall Of Mycobacterium Tuberculosis	59
Tannin	Polyphenolic Compounds		Work Against Mycobacterium Tuberculosis	59

Some plants used to treat Tuberculosis are listed in the Table -V:

Table-V: Medicinal Plants List

Plants	Chemical Constituent	Reference
Allium Sativum	Alkaloids, Flavonoids, Cardiac Glycosides, Terpenes, Resin, Phenol, Aryl, Fats, Fixed Oils	48,49,53,57
Morinda Citrifolia	Alkaloids, Cyanides, Flavonoids, Oxalates, Saponins	48,57
Azadirachta Indica	Flavonoids, Tannins	49
Hygrophila Auriculata	Saponins, Alkaloids, Ecdysteroids, Tannins, Flavonoids, Triterpenoids	49
Chenopodium Ambrosioides	Phenolic Compounds, Flavonoids, Saponins, Steroids, Triterpenoids	49
Solanum Torvum	Sterols, Tannins, Saponins, Flavonoids	49
Phyllanthus Fraternus	Alkaloids, Tannins, Saponins, Terpenoids, Steroids	49
Cyperus Articulates	Terpenoids, Hydrocarbons, Fatty Acids	49
Zingiber Officinale	Tannins, Saponins, Flavonoids, Terpenoids	49
Allium Cepa	Phytohormones, Catechin, Epicatechin, Tannins	49
Moringa Oleifera	Alkaloids, Flavonoids, Carbohydrates, Glycosides, Saponins, Tannins, Terpenoids	50
Glycyrrhiza Glabra	Terpenoids, Alkaloids, Flavonoids, Saponins, Carbohydrates, Isoliquiritigenin, Liquiritigenin	53
Piper Nigrum	Carbohydrates, Alkaloid, Piperine	53,57
Syzygium Aromaticum	Terpenoids, Alkaloids, Flavonoids, Saponins	53
Lawsonia Inermis	Terpenoids, Alkaloids, Saponins, Flavonoids	53
Aegele Marmelos	Terpenoids, Flavonoids, Alkaloids	53
Urtica Dioica	Alkaloids, Flavonoids, Terpenoids	53
Cassia Fistula	Flavonoids	53
Curcuma Longa	Curcumin	52,59
Lantana Hispida	Oleanolic Acid	52
Acalypha Indica	Amine Derivatives	53,57
Camellia Sinensis	Epigallocatechin, Gallate	59
Foeniculum Vulgare	5-Hydroxyfuranocoumarin	52

Advantages of the natural product includes increased safety profiles, hepatoprotective properties, reduces risk of coinfection, increases bioavailability of certain drugs, strengthens immunity. Major disadvantages of natural product-based treatment includes decreased bioavailability and decreased water solubility leading to increased doses that may cause increased side effects, current extraction processes are insufficient to extract and purify crude sources, diversity of molecules and their mechanism of action not fully understood. Lack of clinical trial data, scientific evidence, lack of interaction with drugs are not largely available. Natural product-based treatment can be improved by developing the effective delivery systems such as nanoparticle-based delivery systems and developing and using of -omics technology such as genomics and focused research.

Conclusion

Mycobacterium tuberculosis is one of the bacterial diseases that affect the mankind in decades and WHO pledged to eradicate this disease from the world. Measures have been taken to eradicate before 2047. Many vaccines and drugs which are under different stages of development are also promising the end of tragic TB era. However, optimism should be tempered with caution. Policymakers, researchers, clinicians, patient, corporates cooperation is highly solicited for sustained progress in the eradication of TB.

Mycobacterium tuberculosis treatment often requires multidisciplinary specialist for complicated and co-morbid patients. Natural products can be a good supplement to regular TB treatment. No robust scientific and clinical evidence are available that TB can be treated with natural products alone.

References

1. Shahinda S.R Alsayed and Hendra Gunosewoyo, Tuberculosis: Pathogenesis, Current Treatment Regimens and New Drug Targets, Int. J. of Molecular sciences, Vol. 24, 2023: DOI: 10.3390/ijms24065202
2. I.barberis, N.L.Bragazzi,L.Galluzzo, M.Martini, The history of tuberculosis: from the first historical records to the isolation of koch's bacillus, J. of prev. med. Hyg.,58 (1),2017, E9-E12.
3. Rebecca E.Colman, et.al Detecting rifampin and isoniazid resistance in mycobacterium tuberculosis direct from patient sputum using an automated integrated system, J of linical tuberculosis and other mycobacterial diseases, 27, 2022 https://doi.org/10.1016/j.jctube.2022.100304
4. Funmilayo Grace Boni, Insaf Hamdi, Liadrine Moukendza Koundi, Kanchan Shrestha , Jianping Xie, Cytokine storm in tuberculosis and IL-6 involvement, J of infection, Genetics and Evolution, Vol.97, 2022 : DOI: 10.1016/j.meegid.2021.105166
5. American thoracic society, Centres for disease control and prevention, Infectious diseases society of America: Controlling tuberculosis in the United States, American Journal of Respiratory and Critical care medicine, 172, 2005,1169 – 1227.
6. David P.Maison, Tuberculosis Pathophysiology and Anti-VEGF Intervention, J of clinical tuberculosis and other mycobacterial diseases,27, 2022 : DOI: 10.1016/j.jctube.2022.100300
7. Kabeer K Shah, Bobbi S.Pritt, Mariam P.Alexander, Histopathologic review of granulomatous inflammation, J of clinical tuberculosis and other mycobacterial diseases, 7, 2017,1 – 12.
8. M.J. Kasten, Mycobacteria in the Literature: report 02 – 2016,J of clinical tuberculosis and other mycobacterial diseases, 7, 2017,51 – 52.
9. Steve Black, David E.Bloom, David C.Kaslow, Simone Pecetta, Rino Rappuoli, Transforming vaccine development, Seminars in Immunology, Vol.50, 2020 : doi: 10.1016/j.smim.2020.101413
10. Cara M.Gill, Lorraine Dolan, Laura M.Piggott and Anne Marie McLaughlin, New developments in tuberculosis diagnosis and treatment, Breathe, Vol.18, 2022: doi: 10.1183/20734735.0149-2021
11. Christoph Lange, Dumitru Chesov, Jan Heyckendorf, Chi C. Leung, Zarir Udwadia, Keertan Dheda, Drug-Resistant tuberculosis: An update on disease burden, diagnosis and treatment, J of Asian Pacific society of respirology, 23, 2018,656 – 673.
12. Amita Jain, Rajesh Mondal, Extensively drug-resistant tuberculosis: Current challenges and threats, J of FEMS Immunol med microbio, 53, 2008, 145 – 150.
13. Lovansha Nandlal, et.al, Rapid Molecular Assays for the Diagnosis of drug-resistant tuberculosis, J of Infection and drug resistance, 15, 2022, 4971 – 4984.
14. Jong Geol Jang, Jin Hong Chung, Diagnosis and treatment of multidrug resistant tuberculosis, Yeungnam University Journal of medicine, 2020, 277 – 285.
15. Thi Ngoc Anh Nguyen, Véronique Anton-Le Berre, Anne-Laure Bañuls, Thi Van

Anh Nguyen, Molecular Diagnosis of Drug- Resistant tuberculosis: A literature Review, J of Frontiers in microbiology,10, Article 794, Apr 2019.

16. Eunjin Cho, Su Jin Lee, Jiyoung Lim, Dong Sik Kim, Namil Kim, Han Oh Park, Ji-Im Lee, Eunsoon Son, Sang Nae Cho, Wah Wah Aung, Jong Seok Lee, Evaluation of TBMDR and XDRA for the detection of multidrug resistant and pre-extensively drug resistant tuberculosis, J of clinical tuberculosis and other mycobacterial diseases, 27, 2022 : DOI: 10.1016/j.jctube.2022.100303
17. Sarah K.Broade, Rachel Dwilow, Dennis Kunimoto, Dick Menzies and Faiz Ahmad Khan, chapter-8, Drug – Resistant Tuberculosis, Cannadian J of respiratory, critical care and sleep medicine, 6, No.51, 2022, 109-128.
18. Simon Tiberi, et al, Drug Resistant TB – Latest developments in epidemiology, diagnostics and management, Int. J. of Infectious diseases, Vol.124, 2022, 520 – 525.
19. Kwonjune J.Seung, salmaan Keshavjee and Michael L.Rich, Multidrug -Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis, Cold Spring Harbor Perspectives in Medicine, 5, 2015.
20. Darshanand Maraj, Liane Steiner, Nav Persaud, Essential tuberculosis medicines and health outcomes in countries with a national essential medicines list, J of clinical tuberculosis and other mycobacterial diseases, 27, 2022: DOI: 10.1016/j.jctube.2022.100305
21. Medeline E. Carwile, Natasha S.Hochberg, Pranay Sinha, Undernutrition is feeding the tuberculosis pandemic: A perspective, J of clinical tuberculosis and other mycobacterial diseases, vol. 27, 2022 : DOI: 10.1016/j.jctube.2022.100311
22. Filia Stephanie, Mutiara Saragih, Usman Sumo Friend Tambunan, Recent progress and challenges for Drug-Resistance Tuberculosis treatment, Pharmaceutics, 13, No.592, 2021: DOI: 10.3390/pharmaceutics13050592
23. C. Young , G. Walzl and N. Du Plessis, Therapeutic host-directed strategies to improve outcome in tuberculosis, Springer Nature – Mucosal Immunology,13, 2020,190 – 204.
24. J. Dobner , S. Kaser, Body mass index and the risk of infection - from underweight to obesity, European Society of Clinical Microbiology and Infectious Diseases, 24, 2018, 24 – 28.
25. Jeremiah Chakaya, Bruce Kirenga, Haileyesus Getahun, Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach, J of clinical tuberculosis and other mycobacterial diseases, 3, 2016, 10 – 12.
26. Isano Hase, Katelynne Gardner Toren, Hitomi Hirano, Kimiko sakurai, Takefumi saito and Masahiro Narita, Pulmonary Tuberculosis in Older Adults: Increased Mortality Related to Tuberculosis Within Two Months of Treatment Initiation, J. of Drugs & Aging, 8, 2021, 807 – 815.
27. Isano Hase, Katelynne Gardner Toren, Hitomi Hirano, Kimiko sakurai, Takefumi saito and Masahiro Narita, Pulmonary Tuberculosis in Older Adults: Increased Mortality Related to Tuberculosis Within Two Months of Treatment Initiation, J. of Drugs & Aging,38, 2021, 807 – 815.
28. Rachel Byng-Maddick and Mahdad Noursadeghi, Does tuberculosis threaten our ageing populations?., BMC Infectious Diseases, 16, 2016 : DOI: 10.1186/s12879-016-1451-0
29. Simon AK, Hollander GA, McMichael A, Evolution of the immune system in

humans from infancy to old age, Proceedings of royal society, Proceedings B, 282:20143085.
30. Theodore Wright, Basak Coruh, David Fredricks, Nina Kim, Immune reconstitution inflammatory syndrome associated with disseminated histoplasmosis and TNF-alpha inhibition, Medical mycology case reports, 23, 2019,62 – 64.
31. Arnold T mafukidze, Marianne Calnan, Jennifer Furin, Peripheral neuropathy in prosons with tuberculosis, J of clinical tuberculosis and other mycobacterial diseases, 2, 2016, 5 – 11.
32. Alberto Ortega-Rosales, Nelson Delgado-Torres, Carlos Burneo-Rosales, A rare neurological complication of tuberculosis: Transverse myelitis, ID cases, Vol.17, 2019: doi: 10.1016/j.idcr.2019.e00564
33. Joseph Donovan, Nguyen Truc Thanh, Guy E.Thwaites, Nguyen Hoan Phu, Severe paradoxical reaction in tuberculous meningitis, ID Cases, Vol.23, 2021 : doi: 10.1016/j.idcr.2020.e01009
34. Yuying Lu, Zhongyang Hu, Fuyan Wang, Huan Yao, Haixia Zhu, Zhen wang, Zhisong, Ru Chen, Ding Liu, Woresning CSF parameters after the start of anti-tuberculosis treatment predicts intracerebral tuberculoma development, Int. J. of Infectious Diseases, 101, 2020, 395 – 402.
35. H.Simon Schaaf, Andrea Collins, Adrie Bekker and Peter D.O.Davies, Tuberculosis at extremes of age, Asian Pacific Society of Respirology,15, 2010, 747- 763.
36. Joel Negin, Seye Abimbola, Ben J.Marais, Tuberculosis among older adults – time to take notice, International Journal of Infectious Diseases, 32, 2015, 135 – 137.
37. Massimiliano Lanzafame, Sandro Vento, Tuberculosis-Immune reconstitution inflammatory syndrome, J of clinical tuberculosis and other mycobacterial diseases, 3, 2016, 6 – 9.
38. Ria Bandiara, Astried Indrasari, Anggi Dewi Rengganis, Lilik Sukesi, Afiatin Afiatin, Prayudi Santoso, Risk factors of latent tuberculosis among chronic kidney disease with routine haemodialysis patients, J of clinical tuberculosis and other mycobacterial diseases, 27, 2022 : DOI: 10.1016/j.jctube.2022.100302
39. Sriram Krishnamoorthy, Natarajan Kumaresan, Alimuddin Zumla, Latent tuberculosis infection and renal transplantation – diagnosis and management, international journal f infectious diseases, 80, 2019, 573 – 576.
40. Xin-Xu Li & Xiao-Nong Zhou, Co-infection of tuberculosis and parasitic diseases in humans: a systematic review, BioMed Central Parasites & vectors, 2013 : DOI: 10.1186/1756-3305-6-79
41. Qiyao Chai,Yong Zhang, Cui Hua Liu, Mycobacterium Tuberculosis: An adaptable pathogen associated with multiple human diseases, Frontiers in cellular and infection microbiology, Article 158,8, May 2018 : doi: 10.3389/fcimb.2018.00158
42. Qiyao chai, Lin Wang, Cui Hua Liu, Baoxue Ge, New insights into the evasion of host innate immunity by mycobacterium tuberculosis, cellular and molecular immunology, Springer nature,17, 2020, 901 – 913.
43. Todd A.Black, Ulrike K.Buchwald, the pipeline of new molecules and regimens against drug resistant tuberculosis, J of clinical tuberculosis and other mycobacterial diseases, vol.25, 2021: doi: 10.1016/j.jctube.2021.100285
44. R.Prasad, TB:85% cure rate seen in modified BPaL regimen trial, The Hindu, 30 Jul 2023, Pg.15.

45. Ritu Banerjee, Jeffrey R Starke, What tuberculosis can teach us about combating multidrug-resistant gram-negative bacilli, J of clinical tuberculosis and other mycobacterial diseases,3, 2016,28 – 34.
46. Derek J.Sloan, Geraint R. Davies, and Saye H. Khoo, Recent advances in tuberculosis: New drugs and treatment regimens, Current Respir Med, Rev 201: 10.2174/1573398x113099990017.
47. Yoanna Teneva, Rumyana Simeonaova, Violeta Valcheva and Violina T.Angelova, Recent Advances in Anti-Tuberculosis Drug Discovery Based on Hydrazide-Hydrazone and Thaidiazole Derivatives Targeting InhA, MDPI- Pharmaceuticals, Vol.16, 2023: DOI: 10.3390/ph16040484.
48. Ravi Rai, Herbal remedies in cure of tuberculosis prevalent among ethnic communities in Central India, An International Journal of Tropical Plant Research, 3-2, 2016, 344 – 353.
49. Joseph Mwanzia Nguta, et. al., Medicinal Plants used to treat TB in Ghana, Int. J of Mycobacteriology, 4, 2015, 116 – 123.
50. Neelam Mangwani, et al, Medicinal plants: Adjunct treatment to tuberculosis chemotherapy to prevent hepatic damage, J of Ayurveda and Integrative Medicine, 11, 2020, 522 – 528.
51. J Mohanasundaram, Role of herbs in tuberculosis: A compilation, Ann. SBV, Jul – Dec 2015, 7 – 12.
52. Vivek Kumar Gupta, et al, Plants in our combating strategies against Mycobacterium tuberculosis: progress made and obstacles met, J of Pharmaceutical Biology, 55 – 1, 2017, 1536 – 1544.
53. Ramesh Pandit, Pawan Kumar Singh, Vipin Kumar, Natural Remedies against Multi-Drug Resistant Mycobacterium tuberculosis, J of Tuberculosis Research, 3, 2015, 171 – 183.
54. Bethany G.Elkington, et. al, Biological evaluation of plants of Laos used in the treatment of tuberculosis in Lao traditional medicine, J. of Pharmaceutical Biology, 47 – 1, 2009, 26- 33.
55. Samuel Getachew, et al, Traditional medicinal plants used in the treatment of tuberculosis in Ethiopia: A systematic review, J of Heliyon, 8, 2022, e09478.
56. Silvi Gautam, et al, Medicinal Plants as Therapeutic Alternatives to combat Mycobacterium tuberculosis: A Comprehensive Review, J. of antibiotics, 12, 2023, 1 – 18.
57. InzerGul Afghan, et al, Combine effects of medicinal herbs on Multidrug-resistant tuberculosis or extensively drug-resistant Tuberculosis, J of Emerging Technologies and Innovative Research, 6, May 2019, 591 – 608.
58. Samuel Baker Obakiro, et al, Ethnobotany, ethnopharmacology, and phytochemistry of traditional medicinal plants used in the management of symptoms of tuberculosis in East Africa: a systematic review, J of Tropical Medicine and Health, 48:68, 2020, 1 – 21.
59. Morgan Maiolini, et al, The war against Tuberculosis: A Review of natural compounds and their derivatives, J. of Molecules, 25, 2020, 1 – 24.
60. Xuejiao Huang, et al, Natural products in anti-tuberculosis host directed therapy, J of Biomedicine & Pharmacotherapy, 171, 2024, 1 – 15.
61. Sripathi Chandragupthan, Deep Insight to Mycobacterium Tuberculosis (Mtb): Causes, Symptoms, Diagnostics, Treatment, Risk Assessment & Recent Advances, J of Medical Science and Clinical Research, 11, Nov 2023, 75 -85. DOI: https://dx.doi.org/10.18535/jmscr/v11i11.10

62. Sripathi Chandragupthan, Climate Change and Infectious Vector Borne Diseases: Causes, Transmission, Symptoms, Diagnostics, Treatment & Challenges, J of Medical Science and Clinical Research, 13, Jan 2025, 10 -22. DOI: https://dx.doi.org/10.18535/jmscr/v13i01.03